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THE NON-PROTEIN NITROGEN AND UREA IN THE MATERNAL AND THE FETAL BLOOD AT THE TIME OF BIRTH.

By J. Morris Slemons and William H. Morriss.

(From the Department of Obstetrics and Gynecology, Yale Medical School.)

Chemical analysis of the blood, which has recently been simplified and standardized to provide clinical methods for routine use, affords an approach to problems in fetal nutrition, especially the interchange of foodstuffs and waste products in the placenta. At present the explanation of these phenomena is based upon very few established facts. In their place we have hypothetical suggestions which are difficult of experimental test, for the object of study is inaccessible and the surgical operation necessary to reach it may impair, or completely destroy, the mechanism in question. Moreover, we have not possessed an analytical technique delicate enough to estimate the substances passing from the mother to the fetus, or in the opposite direction. So long as this was true, partially proven or entirely unproven theories were inevitable. Many of these still prevail, although, ultimately, they will probably be shown to be erroneous, perhaps as erroneous as the Hippocratic conception of the origin and function of the placenta.

The placenta, Hippocrates taught, was formed by coagulation of the mother's blood, and constructed so as to unite directly the maternal with the fetal circulation. The mother's blood was said to leave her body and enter the fetus, and subsequently to return whence it came. This explanation was adopted by Galen and by his successors, until, in 1564, Arantius announced his doubts as to a direct vascular connection between the two organisms. In this opinion, however, he stood alone, and although correct, his belief in the integrity of the fetal circulation was not substantiated by an objective demonstration for nearly a century.

In 1660, Harvey described the arrangement of the placental blood-vessels. As a corollary to his demonstration of a partition between the maternal and fetal circulations, some mechanism was required to effect the transfer of substances from one to the other. Consequently, Harvey assumed that the partition itself played this active rôle, performing its work not unlike the walls of the intestine perform theirs.

The existence of the placental partition was shown in the clearest way by the work of John and William Hunter. The credit due them individually is uncertain, for this investigation caused bitter strife between the brothers, and conflicting claims arose. Together, at least, by injecting both uterine and umbilical vessels, they secured unquestionable proof that the mother's blood never entered the fetus, and also that the reverse phenomenon was impossible.

With the help of the microscope and modern histological technique, the anatomical character of the placental partition became established. And, too, there is no longer a question of the path followed by the fetal blood. The two umbilical arteries containing venous blood, enter the placenta from the cord, dividing again and again to form a multitude of capillaries; subsequently, these reunite into a single vessel, the umbilical vein, through which the arterialized blood returns to the fetus.

An extensive vascular bed, chiefly secured by division of the larger fetal vessels into a myriad of smaller ones, is further enlarged by the arrangement of the smallest of these; they form loops which hang toward the maternal blood. The

vascular loops surrounded by connective tissue, which in turn is covered by epithelium, constitute the chorionic villi. These tiny, finger-like projections are immersed in lakes of maternal blood. They act both as receptors of nutriment for the fetus and as its excretory agents. Beyond these facts, knowledge of the physiology of the villi is fragmentary. How substances pass from one circulation to the other through the layers of chorionic connective tissue and epithelium—which, together with the wall of the fetal vessels, constitute the placental partition—is a question answered, thus far, only hypothetically.

1. *The Vitalistic Hypothesis.*—Active participation by the placenta in the preparation of fetal nutriment, as has been said, was first suggested by William Harvey. And recently, his view, amplified to accord with the prevailing theory of ferments, has been the popular one, for Hofbauer and others have demonstrated the presence of enzymes in placental tissue. However, it has not been shown that these lipolytic, diastatic, and proteolytic enzymes are direct agents in the interchange of substances between mother and fetus. They may be connected only with the living processes of the placental tissue.

2. *The Mechanistic Hypothesis.*—In the transmission of some substances a passive part is taken by the placenta which, in other words, behaves as a permeable membrane. Oxygen and carbon dioxide, as we are taught by the experiments of Cohnstein and Zuntz, will pass equally well from mother to fetus or in the opposite direction. Probably, the laws of diffusion also hold true for other gases, as chloroform, ether, and nitrous oxide; but they do not apply to gases like carbon monoxide which enter into chemical combination with hæmoglobin. Cohnstein and Zuntz found, too, that sodium chloride passed the placenta by osmosis. The evidence regarding the transmission of glucose was not conclusive, but here also these investigators believed that the placenta took no active part.

One fact regarding placental transmission was firmly established by the experiments of Gusserow and his associates; provided the placenta was normal, no insoluble substance could pass it. Consequently, it was admitted that the formed elements of the blood were confined to that circulation in which they originated. Women suffering from leukæmia bear infants that present a normal blood picture. And, experimentally, it has been demonstrated that cinnabar, barium sulphate, and other insoluble compounds introduced either into mother or fetus were completely arrested by the placental partition. On the other hand, a variety of soluble substances injected into the mother may be detected in the fetus. From reports of such experiments Kehrer stated in 1907 that 43 substances out of 73 tested passed readily to the fetus. Similarly, many will pass in the opposite direction. Those known to do so are chiefly poisons selected for study, because a toxic action upon the maternal animal assists in determining the result of an experiment. Strychnin, hydrocyanic acid, nicotin, curare, pilocarpin, physostigmin, phlorhizin, sodium sulphate, methylene blue, and epinephrin injected into the fetus enter the maternal circulation.

Except in the case of carbon dioxide, the elimination of fetal waste products through the placenta has not been the subject of serious investigation. From three analyses in which the same quantity of urea was found in the blood of the mother and her newborn infant, Morel and Mouriquand concluded that the placenta was not a barrier to its transmission. And Bang in a long series of analyses included a few samples of blood from the umbilical cord. But beyond brief and casual comments, there are no data regarding the placental elimination of waste products. The suggestion of Halban and Fleck, that the chorionic villi elaborate an internal secretion which controls fetal excretion, rests entirely upon theoretical considerations. "At present," we read in Döderlein's Handbuch der Geburtshülfe (1915), "it is impossible to say more than that fetal waste products make their way to the placenta and through it reach the maternal organism, which subsequently eliminates them."

Since there is little known of the principles involved in the placental interchange and since direct study of the problem by animal experimentation may introduce artificial factors, we have sought clinical data from which the character of this mechanism could be inferred. In this communication we consider the results of analyses to determine the non-protein nitrogen and the urea in the maternal and the fetal blood. As nearly as possible the specimens were obtained simultaneously, just after the birth occurred; in other words, at the end of the second stage of labor. Usually, the fetal blood was secured first, but at most only a few minutes before the maternal. The former was collected from the placental end of the severed umbilical cord which bled into a sterile flask; the latter was aspirated from a vein in the mother's forearm.

A number of analyses indicated that the fetal blood was derived exclusively from the umbilical vein; a result to be expected from the anatomical structure of the umbilical vessels. The two arteries conducting blood from the fetus to the placenta are supplied with thick, muscular coats which, after the infant is born, contract firmly and completely close these vessels. The umbilical vein, on the contrary, remains patent until thrombosis occurs, and consequently hemorrhage from the cord always comes from this source. The analytical results yielded by the blood flowing from the severed end of the cord, and by the blood aspirated from the umbilical vein were identical—a fact which corroborates the conclusion that we were dealing with specimens of blood from the umbilical vein. In the case of the fetus, then, the sample of blood was arterial and came directly from the placenta.

The maternal blood after leaving the placenta had passed through the heart, the lungs and the hand, before a specimen for analysis was secured. During this course, probably there was no change which could be detected by the analytical methods employed. Professor Otto Folin in a personal communication has expressed this opinion regarding the non-protein nitrogen; and Marshall and Davis found the same values for urea in various organs of the body. Moreover, we have compared specimens from the vena cava * and from the peripheral circulation of dogs anæsthetized with ether and

* The caliber of the uterine veins was so small that a specimen sufficient for analysis could not be aspirated.

found practically no difference between them. The following result is typical:

Blood from	Rest-nitrogen.	Urea-nitrogen.	Percentage of urea-nitrogen.
Vena cava.....	34.9 mg.	20.5 mg.	58 per cent.
Femoral vein.....	34.5 mg.	19.3 mg.	58 per cent.

In human subjects, then, we assume a corresponding resemblance between the peripheral and the uterine blood. If there is any difference between the non-protein nitrogen of the blood in the uterine veins and that in the veins of the forearm, it must be very small. The following results, therefore, fairly represent the composition of the blood which in one instance had just left the fetal side of the placenta and in the other instance the maternal side. This inference was verified by an experiment, the details of which will be given later.

The analytical method employed for the estimation of nitrogen was that devised by Folin and Denis. It consists essentially in removing the protein by precipitation with methyl alcohol, and following this procedure with a Kjeldahl on the filtrate. The latter step determines the non-protein or rest-nitrogen of the blood.

The urea was estimated by the urease method of Marshall, with the apparatus devised by Van Slyke and Cullen. The values thus obtained actually include the ammonia, but in normal cases this is of an amount too insignificant for consideration.

The analytical results for both rest-nitrogen and urea-nitrogen are always stated in terms of milligrams of the substance per 100 cc. of blood.

NORMAL CASES.

I Para.

Number.	Source.	Age of mother.	Length of labor.	Rest-nitrogen.	Urea-nitrogen.	*Percentage of urea-n.	Remarks.
1	Mother..	22	12 hrs.	20.2	9.3	46%	No anæsthetic.
	Fetus...			20.5	8.9	43%	
2	Mother..	19	11 hrs.	21.5	....	....	" "
	Fetus...			24.0	....	....	
3	Mother..	27	53 hrs.	26.8	....	....	" "
	Fetus...			28.7	....	....	
4	Mother..	26	50 hrs.	26.5	9.8	37%	Whiffs of chloroform.
	Fetus...			27.2	10.7	39%	
5	Mother..	19	12 hrs.	21.7	9.3	43%	" "
	Fetus...			20.0	8.4	42%	
6	Mother..	22	18 hrs.	25.0	....	....	" "
	Fetus...			27.2	....	....	
7	Mother..	28	16½ hrs.	21.0	....	....	" "
	Fetus...			21.5	....	....	
8	Mother..	25	12 hrs.	33.5	....	....	" "
	Fetus...			34.2	....	....	
9	Mother..	19	5½ hrs.	33.1	....	....	" "
	Fetus...			32.7	....	....	
10	Mother..	31	27½ hrs.	20.5	....	....	" "
	Fetus...			22.0	....	....	
11	Mother..	29	27 hrs.	20.0	9.8	50%	Deep chloroform.
	Fetus...			19.0	11.7	61%	
12	Mother..	24	18 hrs.	23.0	....	....	Nitrous oxide.
	Fetus...			23.0	....	....	
13	Mother..	20	10 hrs.	26.0	....	....	Morphine and tyramine.
	Fetus...			23.0	....	....	
14	Mother..	20	19 hrs.	27.5	....	....	" " "
	Fetus...			28.9	....	....	

II Para.

15	Mother..	32	4 hrs.	22.5	9.8	44%	No anæsthetic.
	Fetus...			22.0	9.8	45%	
16	Mother..	28	9½ hrs.	23.5	10.3	44%	" "
	Fetus...			20.0	8.9	43%	
17	Mother..	25	5 hrs.	21.7	10.2	47%	" "
	Fetus...			21.7	9.3	43%	
18	Mother..	25	9 hrs.	22.3	....	....	" "
	Fetus...			22.5	....	....	
19	Mother..	25	12 hrs.	21.2	8.9	42%	Whiffs of chloroform.
	Fetus...			22.5	10.3	46%	
20	Mother..	22	7 hrs.	28.2	13.5	51%	" "
	Fetus...			26.5	12.1	46%	
21	Mother..	25	9½ hrs.	19.5	8.4	43%	" "
	Fetus...			19.2	7.9	41%	
22	Mother..	22	8 hrs.	18.5	8.4	45%	" "
	Fetus...			18.5	9.3	50%	
23	Mother..	28	9½ hrs.	32.7	....	....	" "
	Fetus...			30.8	....	....	
24	Mother..	26	8 hrs.	26.2	....	....	" "
	Fetus...			24.5	....	....	

III Para.

25	Mother..	24	6½ hrs.	23.5	....	....	No anæsthetic.
	Fetus...			23.7	....	....	
26	Mother..	22	15 hrs.	25.0	....	....	" "
	Fetus...			26.2	....	....	
27	Mother..	34	4 hrs.	26.5	10.8	41%	Whiffs of chloroform.
	Fetus...			27.5	11.7	43%	

IV Para.

28	Mother..	33	4 hrs.	25.7	....	....	No anæsthetic.
	Fetus...			24.5	....	....	
29	Mother..	36	38 hrs.	27.7	13.1	47%	Whiffs of chloroform.
	Fetus...			27.2	13.5	50%	

V Para.

30	Mother..	34	4 hrs.	25.3	....	....	No anæsthetic.
	Fetus...			25.7	....	....	
31	Mother..	30	11 hrs.	29.7	14.0	47%	Whiffs of chloroform.
	Fetus...			24.2	13.5	55%	

VII Para.

32	Mother..	34	10 hrs.	30.0	....	....	No anæsthetic.
	Fetus(1)			30.2	....	....	Twins at term.
	Fetus(2)			30.2	....	....	Normal infants.

VIII Para.

33	Mother..	39	18 hrs.	27.7	11.2	40%	No anæsthetic.
	Fetus...			24.7	9.8	40%	
34	Mother..	39	7 hrs.	32.0	....	....	Whiffs of chloroform.
	Fetus...			32.0	....	....	

IX Para.

35	Mother..	35	15 hrs.	27.7	12.6	45%	Whiffs of chloroform.
	Fetus...			27.5	11.7	43%	

* The figures in this column indicate the amount of rest-nitrogen which is in the form of urea.

Normal values for the non-protein or rest-nitrogen have been established by the consistent results of several investigators, and it appears that during pregnancy the same values

are normal as at other times. In healthy subjects Folin and Denis found from 22 to 26 mg. of rest-nitrogen per 100 cc. of blood. Almost identical results were obtained by Tileston and Comfort, who also demonstrated a rise of 4 or 5 mg. after meals. In non-pregnant women between the ages of 21 and 75 years, Bang observed from 19 to 28 mg.; the average calculated from eight analyses was 23.2 mg.

On the other hand, Landsberg found in 18 cases of uncomplicated pregnancy that the average quantity of rest-nitrogen was 24 mg. A similar result is recorded by Farr and Williams on the basis of eight analyses. The higher figure of Plass, 34.7 mg., is almost certainly explained by the analytical method employed. Our experience indicates that normally the non-protein nitrogen of the blood is quantitatively the same in pregnant and non-pregnant women; and, furthermore, that there is no noteworthy change at the time of labor.

REST-N. OF MATERNAL BLOOD DURING LABOR.

Onset of labor.	End of 2d stage.	Interval between analyses.
mg.	*mg.*	*hrs.*
18.5	20.5	27½
18.7	23.5	9½
26.0	25.0	15
26.7	28.2	7

A series of 35 cases in which a normal pregnancy terminated with spontaneous delivery was studied, and we found that immediately after the fetus was born specimens of the mother's blood contained from 18.5 to 33.5 mg. of non-protein nitrogen. The average was 25.2 mg. So closely does this result agree with the accepted normal that it may seem superfluous to remark that the question of an error referable to the digestion of food does not enter here. Patients have no desire for food during the active part of labor. Our analyses, therefore, are comparable with others which have been made after a suitable period of fasting. Generally, the values fell between 20 and 30 mg., like those previously given for healthy men and women; lower results were obtained twice and higher ones three times.

It is instructive that the duration of labor is without influence upon the rest-nitrogen, for indirectly this fact is related to the problem of eclampsia. That eclampsia depends upon a retention of nitrogenous waste products is a currently accepted hypothesis; and clinical experience teaches that convulsions develop more frequently when labor is prolonged. As there is no nitrogen retention when labor is prolonged, the predisposing factor to eclampsia must lie elsewhere. However, this evidence against the nitrogen hypothesis is indirect, and for its value depends upon the confirmation it gives to analyses made in the course of the disease.

AVERAGE REST-NITROGEN ACCORDING TO PARITY.

Para.	Rest-nitrogen.	Number of cases.
	mg.	
I.	24.8	14
II.	23.8	10
III.	25.0	3
IV.	26.7	2
V.	27.5	2
VII.	30.0	1
VIII.	29.8	2
IX.	27.5	1

The non-protein nitrogen of the blood does not vary with the age of the patient, nor with the number of previous pregnancies. Although the following table indicates a tendency toward an increase in the rest-nitrogen for successive pregnancies, healthy primiparous women, 20 to 25 years of age, presented even higher values than a patient in her ninth labor.

In the fetus, we found practically the same amount of rest-nitrogen as in the mother; the average of 36 determinations was 24.9 mg. Similarly, the extremes encountered (18.5 and 34.2 mg.) correspond with those of the mother's blood. When the cases are examined individually, the very close resemblance between them becomes most apparent. Results differing by not more than a milligram appear in 20 instances; and the maternal rest-nitrogen was slightly higher than the fetal in 9 instances, and slightly lower in 6. Usually the difference was less than 2 mg. per 100 cc.; it was 5.5 mg. at most. A case of twins follows the rule and perhaps best illustrates it: the mother's blood contained 30 mg., that of each fetus 30.2 mg.

It is reasonably certain that all the constituents of the non-protein blood nitrogen may pass through the placenta, for they belong either to the class of foods or of waste products. The fetus acquires its nitrogenous food from the mother and after utilization the resulting waste is transferred to her circulation. Equal values for the rest-nitrogen on both sides of the placental partition indicate a free interchange of these substances, probably by diffusion. Accordingly, active participation of the placental partition would not be required; the interchange of a substance would depend merely upon its concentration in each circulation. The interpretation of the analytical results certainly does not require the agency of placental enzymes. But before diffusion is accepted as the explanation for the placental interchange of non-protein nitrogen, each of its constituents—urea, ammonia, uric acid, creatinin, and amino acids—should be studied separately. As regards the urea and ammonia, we have data which demonstrate that these substances diffuse readily through the human placenta.

The urease method, as we have said, yields results which embrace both the urea and the ammonia, but normally the blood contains an extremely small quantity of the latter, which, therefore, may be disregarded. Conforming to the custom adopted in similar reports we designate the urease determinations, "urea-nitrogen." Yet, for our purpose, they have a broader significance, indicating that not only the urea but also the ammonia of the blood passes the placenta by diffusion.

In 16 normal cases at the moment of birth the average quantity of urea-nitrogen in the mother's blood was 10.5 mg.; and in the fetal blood 10.4 mg. The extremes encountered corresponded closely; in the mother they were 8.4 and 14.0 mg., and in the fetus 7.9 and 13.5 mg. And again, examined case by case, the urea values in mother and fetus are equivalent. Thus, the determinations were identical in 11 instances, while

there was slightly more maternal urea in 3 instances and slightly more fetal urea in 2. The maximal difference between them was 1.9 mg. per 100 cc.

UREA-NITROGEN IN MATERNAL AND FETAL BLOOD AT THE MOMENT OF BIRTH.

Para.	Mother.	Fetus.	Number of cases.
	mg.	*mg.*	
I.	9.6	9.9	4
II.	9.9	9.7	7
III.	10.8	11.7	1
IV.	13.1	13.5	1
V.	14.0	13.5	1
VIII.	11.2	9.8	1
IX.	12.6	11.7	1

There is abundant evidence to show that urea is a readily diffusible substance in the animal body. Bang found equal quantities in corpuscles and plasma. Marshall and Davis demonstrated that the same concentration existed in the blood and tissues, both normally and after large injections of urea. The latter investigators concluded that diffusion was almost instantaneous and after 15 minutes was complete. Upon these premises it would be fair to assume that the analytical results obtained from the blood of the arm veins also applied to the blood in the uterine veins, returning from the placenta after participation in the interchange between mother and fetus. But we have verified the accuracy of this assumption. In the case of an etherized dog near term, specimens of blood from the uterine and umbilical veins were analyzed. The results confirm our clinical observations and also agree with two experiments upon rabbits made by Morel and Mouriquand, though these investigators do not mention the source of their specimens.

MATERNAL AND FETAL BLOOD OF DOG.*

Source.	Rest-nitrogen.	Urea-nitrogen.	Per cent urea.
Uterine vein	40.0 mg.	16.4 mg.	41
Umbilical vein..	41.5 mg.	16.4 mg.	39

* Higher values occur in dogs because they are carnivorous.

Normally, then, the same concentration of urea exists in the maternal and fetal circulations; and this is also true of the ammonia, for the analytical method yields results that include both substances. Maintenance of this equilibrium requires the freedom of movement permitted by diffusion. Indeed, the question of an enzyme action can scarcely come into consideration, since there is no notable difference in the urea concentration on the two sides of the placenta.

Morel and Mouriquand also obtained similar values for the amino acids in maternal and fetal blood; and consequently stated that the placenta is not a barrier to the passage of nitrogenous crystalloids. In this laboratory, Morse has estimated the amino-acid nitrogen in the blood of mother and fetus; and though his results, which will soon be published, suggest that that problem is more complex than the urea problem, it appears that maternal and fetal blood contain equivalent amounts of amino acids. Creatinin and uric acid remain unstudied.

It is noteworthy that at the time of labor the quantity of urea in the blood is the same as during pregnancy, and that this quantity is somewhat less than the accepted normal. Employing the urease method, Schwartz and McGill found 12.9 mg. the average for healthy subjects; with other methods Folin and Denis found 11-13 mg., Tileston and Comfort 12-14 mg. Bang found 12.3 mg. as the average for eight normal women. On the other hand, Farr and Williams obtained 10.7 mg. during pregnancy, which is practically the average calculated from our series of normal labors.

In healthy men and women, the urea includes approximately 50 per cent of the total non-protein nitrogen, but at the time of labor this percentage is smaller. For the mother the urea represented 44 per cent of the rest-nitrogen and for the fetus 45 per cent. The latter figure closely resembles the average which Leopold and Bernhard found in children. There the rest-nitrogen was 28 mg., the urea-nitrogen 12 mg., and consequently the ratio between them was 43 per cent.

ABNORMAL CASES.

OBSTETRICAL OPERATIONS.

Number.	Source.	Age of mother.	Duration of labor.	Rest-Nitrogen.	Urea-Nitrogen.	Percentage of urea-n.	Remarks.
		yrs.	*hrs.*	*mg.*	*mg.*		
36	Mother.	27	9¼	22.7	11.2	49	Low forceps; chloroform.
	Fetus..	IIp.		22.7	11.2	49	Normal infant.
37	Mother.	20	21½	20.5	12.6	61	Mid-forceps; chloroform.
	Fetus..	Ip.		20.5	14.9	72	Cord about neck; resuscitated.
38	Mother.	23	48	37.5	28.0	74	Attempts at forceps; prolonged
	Fetus..	Ip.		36.0	30.1	85	chloroform. Craniotomy.
39	Mother.	28	13	26.5	14.9	56	Spontaneous delivery; deep
	Fetus..	IIp.		21.0	14.9	71	chloroform; asphyxiat. infant.
40	Mother.	22	48	27.0	13.5	50	Low forceps; ether.
	Fetus..	Ip.		30.0	14.1	47	Normal infant.
41	Mother.	22	54½	25.5	11.7	46	Breech. Chloroform.
	Fetus..	Ip.		20.2	13.1	65	Still-birth.
42	Mother.	24	24	34.2	....	.....	Breech. Chloroform.
	Fetus..	IVp.		34.2	....	.....	Normal infant.
43	Mother.	35	9	21.2	15.8	74	Version. Chloroform.
	Fetus..	Vp.		24.2	15.8	65	Still-birth.

PREGNANCY TOXÆMIAS.

44	Mother.	20	28	21.2	13.1	61	Pre-eclamptic tox. Forceps.
	Fetus..	Ip.		22.7	12.6	55	Healthy, premature infant.
45	Mother.	35	...	34.0	30.1	88	Pre-eclamptic tx. Hysterotomy.
	Fetus..	IIp.		35.5	26.1	74	Premature.
46	Mother.	33	...	31.0	12.6	46	Eclampsia; Caesarian; ether.
	Fetus..	IIIp.		30.7	....	.....	Premature.
47	Mother.	24	16	45.7	28.4	62	Eclampsia; high forceps. Died.
	Fetus..	Ip.		43.5	27.1	62	Still-birth.
48	Mother.	42	8	33.3	....	.....	Chr. nephritis. Mid-forceps.
	Fetus..	XIIp.		40.0	....	.....	Still-birth.
49	Mother.	42	6	....	18.2	.....	Chr. nephritis; normal labor.
	Fetus..	XIIIp.		....	16.8	.....	Normal infant.

SYPHILIS.

50	Mother.	20	8¼	24.0	13.6	57	At term.
	Fetus..	Ip.		24.0	14.0	58	Infant alive.
51	Mother.	21	11½	21.2	11.0	51	At term.
	Fetus..	Ip.		20.0	10.4	51	Infant alive.
52	Mother.	20	6½	....	20.7	.....	Premature delivery, 7th month.
	Fetus..	IIp.		....	20.1	.....	Died shortly after its birth.
53	Mother.	19	22½	27.0	14.9	55	Wassermann neg.; placenta syphilitic.
	Fetus..	Ip.		24.5	14.0	57	Infant normal.

PSYCHOSIS.

54	Mother.	36	12	25.0	14.9	60	Imbecile mother.
	Fetus..	Ip.		25.0	14.9	60	Premature, poorly nourished.

CARDIAC LESIONS.

55	Mother.	22	16	28.7	17.7	62	Mitral and aortic regurgitation.
	Fetus..	Ip.		21.7	14.9	54	Normal infant.

STILL-BORN INFANTS.

56	Fetus..	.....	69	22.5	14.0	62	Face presentation; forceps.
57	Fetus..	.....	62	20.7	15.4	74	Mid-forceps; chloroform.
58	Fetus..	.....	50	26.7	13.0	49	Enlarged thymus.

AVERAGE OF NORMAL CASES *with* AND *without* CHLOROFORM.

	Rest-nitrogen.		Urea-nitrogen.		Percentage of urea-nitrogen.	
	Mother.	Fetus.	Mother.	Fetus.	Mother.	Fetus.
	mg.	*mg.*	*mg.*	*mg.*		
No anæsthesia.....	23.1	21.6	10.1	9.3	44	43
Whiffs of chloroform.....	24.3	23.6	10.5	10.9	43	46

In a number of instances in which complications existed we have had the opportunity to make observations comparable with those made during normal labor. Thus data were obtained relating to chloroform anæsthesia, obstetrical operations, syphilis, the autointoxications of pregnancy, and asphyxiation of the fetus during delivery. On their own account, these results were instructive and also because they gave additional information regarding the problem of the placental interchange.

Chloroform anæsthesia interferes with the nitrogenous exchange between mother and fetus, not when administered in whiffs as customarily at the conclusion of the expulsive stage of labor, but if given to maintain deeper anæsthesia. The effect varies with the depth and the duration of narcosis. Among cases in the normal series some of the deliveries were conducted without an anæsthetic, others with chloroform. The averages of these groups are not unlike, and demonstrate that the effect of the (so-called) obstetrical degree of chloroform narcosis upon the non-protein nitrogen of the blood is negligible. Somewhat deeper anæsthesia also is attended only with slight alterations in the composition of the fetal blood. Case 11 illustrates this point. For 15 minutes before the birth the mother was completely anæsthetized: the infant was not asphyxiated; its blood contained a normal amount of rest-nitrogen and 61 per cent of urea-nitrogen. Although less conspicuous, a tendency for the urea to increase is apparent in the average of the normal cases given chloroform. This feature is pronounced in Case 39 (71 per cent of fetal urea-nitrogen) where fetal asphyxia was relieved only after vigorous resuscitative measures.

Surgical anæthesia is accompanied with an elevation also in the maternal urea, and ultimately with increase of the non-protein nitrogen in both circulations. Case 38 exemplifies these effects. In this instance, before the patient entered the hospital, several attempts with forceps had been made and she had been under chloroform for a period of about two hours. The maternal nitrogen was 37.5 mg., and the urea-nitrogen 28 mg., the fetal nitrogen was 36 mg. and the urea-nitrogen 30.8 mg. Whether these effects are partially to be explained by the operative procedure is a question difficult to answer, but generally such changes are not the sequel of a forceps operation. For example, Case 36 presents only a slight increase in urea, which corresponds with that referable to the use of chloroform in normal cases.

From our observations, then, it appears that at first chloroform merely increases the fetal urea. This phenomenon we do not attribute to an increased production of urea in the fetus but to a diminished rate of diffusion through the placenta. Clinically, it is known that chloroform slows the fetal heart and consequently in a given length of time a smaller quantity of blood reaches the placenta. In these circumstances, obviously, fetal urea has less opportunity for excretion. Later, principally because of urea retention, the rest-nitrogen of the fetal blood increases. Irrespective of the fetus, deep chloroform anæthesia finally causes an increase of both urea and rest-nitrogen in the maternal circulation. However, even with prolonged anæsthesia the effect upon the fetus is the more pronounced.

In cases in which low forceps operations were performed because the expulsive forces were insufficient, we found nothing notable beyond the initial, mild effects of chloroform. After this operation, indeed, we found less marked changes in the fetal blood than when pituitrin was used to augment uterine contractions. Thus, in a case of the latter kind, the fetal urea was 14 mg., whereas after low forceps we observed 11.2 and 11.7 mg. On the other hand with medium and high forceps, requiring deeper and more prolonged anæthesia, the fetal urea-nitrogen amounted to 13, 14, and 15 mg.

As anyone would predict, we found that coils of cord about the neck of the fetus constricting the umbilical vessels caused retention of urea in the fetal circulation. This occurred in Case 37, although the interpretation of the analysis is complicated by the fact that the patient was deeply anæsthetized. A more marked contrast between mother and fetus existed in the case (No. 41) of breech extraction, where the umbilical circulation was shut off for several minutes and the fetus was still-born.

During the autointoxication which precedes eclampsia and also after the development of convulsions, blood analyses have failed, thus far, to render assistance toward either treatment or prognosis. At times, though not invariably, there is a moderate increase in the non-protein nitrogen—a phenomenon that must be explained by the degree of renal involvement. In this sense, Cases 44 and 45 present an interesting contrast. The former was a typical case of pre-eclamptic toxæmia with moderate elevation of blood-pressure and mild albuminuria. The latter patient suffered from a pronounced renal disturbance; the urine contained 10 gm. of albumin per liter and the systolic pressure was 200 mm. of mercury. In the first case, though the urea (13 mg.) was slightly increased, the rest-

nitrogen (21 mg.) was normal; in the second case the urea was 30 mg. and the rest-nitrogen 34 mg.

With regard to placental transmission, cases of renal insufficiency demonstrate that high urea values in the maternal circulation are accompanied by corresponding values in the fetal circulation; a finding which confirms the conclusion that urea passes the placenta by diffusion. Furthermore, in other pathological conditions attended by an increase in the maternal blood-urea, a similar increase appears in the fetus. Whether the fetal values are explained by the passage of urea from mother to fetus—as Cohnstein and Zuntz showed to be possible in the case of carbon dioxide—or whether the high concentration of urea in the mother's blood merely prevents diffusion in the normal direction, is a question to be settled by animal experimentation. However, in either event the result for the fetus is the same and means an impairment of the placental excretory function. Clearly, this may be of a degree to cause intrauterine death, a well-known complication in cases of nephritic toxæmia, which occurred in Case 48.

As already observed by Tileston and Comfort and by Schwartz and McGill, abnormally large quantities of urea occur in syphilitic patients, yet not without exception (Case 51). Our chief interest is in the fact that when the mother presents the phenomenon, so does the fetus. And, similarly, in Case 54, in which the mother was suffering from an undetermined organic disturbance—probably of the ductless glands—with consequent low mentality, placental diffusion satisfactorily accounts for the duplication in the fetus of a high maternal urea.

The analyses in a case (No. 55) of combined mitral and aortic disease are noteworthy. About eight weeks before confinement compensation had been broken but later was restored. Toward the end of labor the patient became exhausted. Much higher urea values than were present in this instance (17.7 mg.) have been shown to be due to cardiac decompensation by Foster, by Rountree, Marshall and Baetjer and by Schwartz and McGill. The maternal heart action must also account for an increase in the fetal urea, since at birth and subsequently the infant's physical condition was excellent.

ASPHYXIATED AND STILL-BORN INFANTS.

No.	Rest-nitrogen.	Urea-nitrogen.	Percentage of urea-nitrogen.	Remarks.
	mg.	*mg.*		
37	20.5	14.9	72	Cord about neck; resuscitated.
39	21.0	14.9	71	Mid-forceps; resuscitated.
57	36.0	30.1	85	Mid-forceps; still-born.
38	20.7	15.4	74	High forceps; still-born.
41	20.2	13.1	65	Breech; still-born.
43	24.2	15.8	65	Version; still-born.
48	40.0	....	..	Nephritic tox.; still-born.
56	22.5	14.0	62	Face presentation; still-born.
58	26.7	13.0	49	Enlarged thymus.

In cases of fetal asphyxia and still-birth the results of the blood analyses are consistent and indicate that, although the non-protein nitrogen is generally of normal amount, the urea is increased. These facts are best explained by the circulatory phenomena which accompany fetal death. Slowing of the fetal heart, as we have said, lessens the rate at which the fetal blood flows through the placenta, and correspondingly impedes the placental interchange. At first, urea is retained in the fetal blood without increasing the rest-nitrogen, for probably the excess of urea is counterbalanced by a deficiency in amino acids, the supply of which is curtailed when the fetal circulation becomes less active. Subsequently, an increase in urea causes an increase in the rest-nitrogen.

While the average quantity of urea-nitrogen in normal fetal blood is 10.5 mg. the lowest estimate among six still-born infants was 13 mg., the highest 30 mg. However, there was not a sharp line between cases of asphyxia and still-birth; 15 mg. were found in each of two asphyxiated infants which were resuscitated, and this was a larger quantity than obtained in three of the still-births.

Besides circulatory impairment, other causes of fetal asphyxia, as in Case 58, occasionally are met with. In this case the fetal heart was beating normally at birth, but the infant could not be made to breathe. An autopsy disclosed a thymus several times the normal size. Thymic death, it would seem, depends upon the respiratory center, not upon a circulatory disturbance, for the heart was active half an hour after the birth. Moreover, the relationship between the urea and rest-nitrogen was not abnormal; there were 13 mg. of urea-nitrogen, representing 49 per cent of the rest-nitrogen. On the other hand, with circulatory impairment the urea has represented from 60 to 85 per cent of the rest-nitrogen in the fetal blood.

SUMMARY.

1. In 35 normal obstetrical patients at the time of birth the average rest-nitrogen in the maternal blood was 25.2 mg. per 100 cc. (extremes 18.5-33.5 mg.); in the fetal blood the average was 24.9 mg. (extremes 19-34.2 mg.).

2. In 16 normal patients the average quantity of urea-nitrogen in the maternal blood was 10.5 mg. per 100 cc. (extremes 8.4-14 mg.); in the fetal blood the average was 10.4 mg. (extremes 7.9-13.5 mg.).

3. The urea-nitrogen represented 44 per cent of the rest-nitrogen in the maternal and 45 per cent in the fetal blood.

4. The same concentration of urea in both circulations indicates that this substance passes through the placenta by diffusion.

5. Before this is said of the rest-nitrogen, each of its constituents should be studied separately, though it appears that equalization of the rest-nitrogen is normally maintained on the two sides of the placental partition.

6. Complications accompanied by an increase of urea in the maternal blood—toxæmias of pregnancy, syphilis, decompensated heart lesions, and others—are also attended with a corresponding increase in the fetal blood-urea. Pathological cases thus confirm the conclusion that urea diffuses through the placenta.

7. The administration of chloroform during pregnancy causes alterations first in the fetal and later in the maternal blood. Primarily the fetal blood-urea is increased. Prolonged

anæsthesia causes a moderate increase in the rest-nitrogen of both circulations.

8. Asphyxia dependent upon impairment of the fetal heart-action is attended with a notable increase in the urea of the fetal blood. In cases of still-birth this generally represents 60 to 85 per cent of the rest-nitrogen.

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TYPES OF LESION IN CHRONIC PASSIVE CONGESTION OF THE LIVER.

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It is generally recognized that the so-called "nutmeg liver" of chronic passive congestion presents a varied microscopic picture. Indeed, two livers, which to any but the most experienced observer are identical in gross appearances, may show most striking histological differences. In one the lesion may consist of a marked dilatation of the capillaries, especially in the immediate neighborhood of the central vein, with an elongation and narrowing of the intervening liver cells; in the other, the liver cells of the inner half or two-thirds of the lobule may have entirely disappeared, this area being occupied by blood, reticulum and occasional pigmented endothelial cells. The study of even a limited number of livers from cases of cardiac decompensation will soon convince one that these two types of lesion constitute by no means the only possibilities.

The object of the present study was first to classify, if possible, the varied liver lesions in chronic passive congestion. This accomplished, we attempted to determine the conditions responsible for the development of the different types, through a consideration of both clinical and autopsy findings.

Before describing the results of our investigations a brief statement of the present teaching regarding the character of the liver lesions in chronic passive congestion, and their pathogenesis, will be briefly presented, together with a review of the more important contributions to this subject.

It was for a long time the accepted view that the disappearance of the liver cells in advanced chronic passive congestion resulted from increased blood pressure in the capillaries. Among the adherents of this theory may be mentioned Orth, Birch-Hirschfeld, Marchand and Kaufmann. Ribbert was among the first to recognize the objection that increased blood pressure must be transmitted throughout the lobule, and obviously cannot be higher in the center than in the periphery; its effect should, therefore, be diffuse, whereas it is the central portion of the lobule that regularly suffers most in chronic passive congestion. Ribbert pointed out further that the cells that succumb are those farthest removed from the blood supply, and suggested that these cells suffered from malnutrition resulting from stasis, which rendered them more susceptible to increased pressure. The process is thus regarded by him as a combined starvation and pressure atrophy. Other authors, including Sternberg and Eisenmenger, have in a general way accepted Ribbert's dualistic theory, putting emphasis on one or the other of the two factors.

The formation of fibrin thrombi in the liver capillaries, favored by the retardation of the blood flow, has been suggested as the cause of the death of the liver cells in chronic stasis, but Hart,

Hajami, Mallory and L'Engle, agree in regarding the thrombus formation as the effect rather than the cause of the necrosis. L'Engle, indeed, believes that the fibrin plugs are formed after death. In our cases thrombi were commonly met with, but they were not a constant finding, and were not associated with any particular type of lesion.

Mallory has recently brought forward an entirely new interpretation of the changes in the liver in chronic passive congestion, and goes further than Ribbert, Eisenmenger and Sternberg in minimizing the effect of increased blood pressure. He maintains that blood pressure is not a factor at all. In his opinion, based on a clinical and pathological study of a large number of cases, the disappearance of the liver cells is practically always the result of a toxic necrosis, and the stasis is only a contributory factor. He points out that while long continued stasis may lead to extreme dilatation of the sinusoids, the flattening out of the intervening liver cells, and complete atrophy or necrosis, probably never take place as the result of increased blood pressure alone. "Necrosis" he states, "is due to toxic substances (chiefly of infectious origin) in the circulation, acting apparently to some extent in combination with malnutrition. In many instances the necrosis complicating chronic passive congestion is due to the terminal infection which causes death. In others, the necrosis and disappearance of the liver cells dates back to some infection which occurred months or years previously." Mallory points out, in support of this view, that in acute infections (especially streptococcic) not associated with stasis, degenerative changes in the liver cells about the center of the lobule are frequently seen. He grants that the hemorrhagic character of the lesion is the result of stasis, since the blood from the distended capillaries pours readily into the ruptured trabecular spaces—among the dead and disintegrating liver cells. The familiar picture of hemorrhagic necrosis is the result.

This new interpretation of the pathogenesis of the lesion of chronic passive congestion has met with ready acceptance by Heinrichsdorff, in a recent paper. Bolton, however, on the basis of experimental studies, concludes that stasis, with resulting malnutrition, is the essential cause of the disappearance of the liver cells. He produced a condition of chronic stasis in monkeys and cats by incomplete obstruction of the inferior vena cava. The typical picture of chronic passive congestion resulted, ending in central necrosis with hemorrhage. His animals remained perfectly healthy throughout the experiments and showed no evidence whatever of infection. Oertel, who has studied especially the jaundice occasionally associated with chronic stasis, regards the death of the liver cells as the direct result of the congestion and as in no way referable to bacterial injury. MacCallum, accepting the arguments against the theory of pressure atrophy, is also inclined to regard stasis itself, with the consequent poor nutrition —or rather, poor oxygenation—of the cells farthest from the arterial blood supply, as the essential etiological factor.

In undertaking this investigation, we were fortunate in having at our disposal a large number of cases for study, with clinical histories, autopsy protocols, and tissue for microscopical examination, there being nearly 600 cases of all kinds at the Presbyterian Hospital and 50 cases at the Montefiore Hospital. Among these were 112 cases of well marked chronic passive congestion. In most instances the stasis was the result of some lesion in the heart or blood-vessels, but a number of other diseased states were represented—emphysema, chronic pulmonary tuberculosis, pernicious anemia, etc.—in which, as has been recognized, a condition of chronic stasis may be present.

GROSS CHANGES IN THE LIVER.

Among over 112 cases of chronic passive congestion there were 53 gross specimens. Twenty-three of these were fresh organs examined at the autopsy table; the remainder were museum specimens preserved in Kaiserling's solution. They varied considerably in size, color and consistence, but the majority were fairly typical "nutmeg" livers. The average weight of 66 specimens from adults was 1622 gm.; the extreme weights were 1010 and 2830 gm. The latter specimen was a very fatty organ. The weights of many would have been considerably greater had the blood not been allowed to drain out. The shrinkage after the vessels were cut was sometimes considerable. The smaller livers came usually from cases of long continued stasis, which showed microscopically much loss of liver substance with collapse. In the larger specimens fatty changes or extreme grades of cloudy swelling were nearly always seen. While the majority of the specimens were typically mottled organs, with distinct but often irregular lobulation on the cut surface, the gross appearance even in these varied considerably. In the same organ the picture was often very different in different parts. In general the stasis was most marked at the surface of the liver, or near the hilum, as indicated by the deep red color of these portions. Large, sunken, purplish red areas, with only small islands of gray surviving parenchyma about the portal spaces, were sometimes seen. In other parts of the same liver large, pale, elevated patches of parenchyma might be found. In the latter the lobulation was often indistinct, and such areas have been interpreted as regenerating nodules of liver tissue. (See Fig. 601, p. 839, in Aschoff's Text-book of Pathology, Vol. II, 1911.) After studying microscopically a number of such areas, we have been convinced that they do not represent large patches of regenerated liver tissue, but are simply groups of lobules in which the stasis is much less marked.

That regenerative changes do occur in chronic passive congestion is well known, but in all of our cases in which microscopic evidences of regeneration were found—mitosis, large multi-nucleated cells, asymmetrical lobules—the regenerative changes were never sufficient to form gross nodules of new liver tissue. The regeneration was insignificant as compared with the nodular hyperplasia often seen in portal cirrhosis. It may be mentioned here that regenerative changes were found only in cases of long standing, and were surprisingly rare in livers showing extensive hemorrhagic necrosis. Contrary to the common teaching we have found hyperplasia more often in middle-aged or in elderly individuals than in the young. This is probably due to the fact that examples of long-standing congestion are found more often in older people.

In nine out of the 112 cases studied, definite jaundice of the liver (and to a less degree of the other organs) was noted. It would seem probable, as Oertel has maintained, that the bile stasis in these cases was the result of a necrosis of the liver cells. It may be pointed out, however, that a microscopical study of livers shows in several of the jaundiced specimens little or no necrosis. On the other hand, widespread necrosis

was found in several in which there was no evidence of bile stasis.

Even after we had made a comparative study of our 53 specimens, it was difficult to group them on the basis of gross features. Certain extreme types were recognizable, however; for example, those showing marked central fat accumulation with mid-zonal hyperemia (Type III, described below) could be easily recognized. Also, the old, firm, collapsed organs (Type V, described on page 353). The commoner types, on the other hand, showing microscopically either marked dilatation of the sinusoids (Type I) or central hemorrhagic necrosis (Type IV, described on page 353) are difficult or impossible to distinguish.

MICROSCOPICAL CHANGES IN THE LIVER.

Two types of lesion have already been mentioned—(a) capillary dilatation, with narrowing and elongation of the liver cords (so-called pressure atrophy), and (b) central necrosis with hemorrhage. A careful study of our cases has convinced us that at least three other types—five in all—may be recognized. So many subdivisions of what is generally discussed as one lesion may not seem warranted. We have, however, convinced ourselves that clear-cut differences in the types described do exist. In going over our cases independently from time to time we rarely made any change in the grouping of a particular case. It should be pointed out, however, that pure types are not the rule, and that transitions are not infrequently encountered.

Type I. Capillary Dilatation with Atrophy of Central Cells (33 cases, or 30 per cent of the total number).—In this type of lesion the microscopical picture is that described in many of the text-books as characteristic of marked passive congestion, and it is the lesion on which was based the older idea that the liver cells in extreme stasis disappeared as the result of pressure atrophy. Certainly the dilatation of the sinusoids, with elongation of the cells (Fig. 1), does give the impression that the cells are compressed. Dilatation of the capillaries throughout the entire lobule is sometimes seen, but it is always most marked near the center of the lobule. That there is atrophy of the liver cells, it seems to us, can scarcely be questioned. The cells are distinctly smaller than normal, being sometimes reduced to mere strands. Degenerative changes, however, are not infrequently seen, and there can be no doubt that necrosis with hemorrhage does sometimes take place, as in Type IV, described below. Since this type of lesion, unassociated with degenerative or necrotic changes, is seen in less than a third of the cases of chronic passive congestion, it is obvious, as Mallory has pointed out, that undue emphasis has been placed upon it in the text-books. Furthermore, it is not the type of lesion found in extreme stasis resulting, for example, from advanced cardiac valvular disease, but is found most often in cases of moderate circulatory disturbance of long standing, as in arteriosclerosis, chronic nephritis or some debilitating disease, such as chronic pulmonary tuberculosis. Widespread dilatation of the capillaries is apparently a slow process. Severe or rapidly developing circulatory disturbance leads usually to necrosis with hemorrhage, as we shall point out later.

Type II. Central Degenerative Changes with or without Congestion (21 cases, or 18 per cent of the total number).—In this lesion (Fig. 2) the number of cells affected varies as in Type I; usually about one-half, or more, of the lobule is involved. The dividing line between healthy and degenerated liver cells is often quite sharp. The affected cells are reduced in size. The cytoplasm stains pink with eosin, and is often finely vacuolated and pigmented. Although the cells are small, the capillaries between the cell cords may not be dilated. On the contrary, they often appear narrow, apparently as the result of a sub-endothelial accumulation of fluid (edema), a condition to which Mallory and others have called attention. Although necrosis with hemorrhage is sometimes noted in places, the lesion is generally seen as a pure type. It corresponds closely to that described by Mallory as central necrosis without hemorrhage. But we have avoided the term "necrosis," because the cells are not dead, the nucleus is well preserved and stains normally, and the cell membrane is intact. Livers showing definitely necrotic cells have been placed in another group (Type IV).

This lesion was not associated with any particular disease of the circulatory system. It was found in cases of cardiac valvular disease, advanced myocardial fibrosis, chronic nephritis with cardiac failure; occasionally also in pernicious anæmia and severe acute infections. In general it may be said that in cases showing this type of lesion there is either a well marked, though not extreme, disturbance in circulation, or else there is a condition of moderate stasis, complicated by acute infection.

Type III. Central Fat Accumulation with Mid-Zonal Hyperæmia or Necrosis (9 cases, or 8 per cent of the total number).—The microscopic picture is very striking (Fig. 3). There is a zone of large fatty cells, with well preserved nuclei immediately surrounding the hepatic vein. The capillaries in this area are scarcely visible, as though compressed by the swollen liver cells which seem to be especially resistant. In the adjacent middle zone, however, capillaries are widely dilated, and liver cells are smaller and less fatty, giving an appearance similar to that about the center of the lobule in Type I. Not infrequently foci of necrosis are encountered with hemorrhage into the trabeculæ as in Type IV. This type of lesion was mentioned by Mallory, and is thoroughly described by Heinrichsdorff, who applied to it the name "ring necrosis." Heinrichsdorff emphasizes the striking gross appearance of the liver—a tiny yellow spot, in which the hepatic vein is scarcely visible, forms the center of each lobule, and immediately surrounding it is a red zone or ring (hence the name "ring necrosis"), and outside that healthy liver parenchyma about the portal spaces. These gross characteristics were noted in all of our specimens, and served to differentiate them readily from other types. All of the nine livers in this group were found in cases of chronic rheumatic endocarditis, and nearly all were in individuals under 20 years of age (Cases 6 and 7). A larger series of cases will probably be necessary to determine whether this is a constant relationship.

Type IV. Central Necrosis, Usually Associated with Hemorrhage (33 cases, or 30 per cent of the total number).—Under the low power of the microscope the center of the lobule in typical examples of this lesion looks like a homogeneous mass of fresh blood; an occasional pigmented endothelial cell is visible (Fig. 4). Under higher magnification, fragments of necrotic liver cells, and the surviving reticular fibers, can be made out. The necrosis may involve only a narrow zone about the central vein, or may be so extensive as to leave only a few healthy liver cells at the margin of the lobule (Fig. 5). The necrosis ends abruptly, passing over into a narrow zone of fatty cells, which in turn merges into a mantle of normal cells around the portal spaces (Fig. 4). The early stage of this lesion has been well described by Mallory, who first recognized the picture as a true necrosis with hemorrhage into the trabecular spaces. In the majority of cases liver cells have completely disappeared, but we were fortunate in finding two in which the necrosis was very recent, and the bodies of the dead cells still remained more or less intact, with little hemorrhage. The cases throw light on the etiology of the lesion about which there has been a good deal of dispute. Each of the patients had been suffering for a considerable time from "heart trouble," with mild symptoms of circulatory failure. One patient (Case 9, see protocol) developed suddenly, seven days before death, signs of cardiac failure, which increased progressively until death. The other, an elderly man, who was also living a comfortable life, collapsed suddenly 11 days before death. In each of these cases arteriosclerosis of the coronaries was found at autopsy, with recent thrombosis of one of the larger branches. In neither was there a terminal complicating infection. These two cases afford definite proof that necrosis of liver cells may be caused by stasis alone. This conclusion has been more firmly established by a tabulation of our entire series of cases with regard to the existence of terminal or recent infections. Briefly stated, it was found that the percentage of infections, including pneumonia, pleurisy, peritonitis, meningitis and sepsis, was practically the same in Type I, where no necrosis was observed, as in Type IV, hemorrhagic necrosis. Ten cases of bacteriæmia, staphylococcic, steptococcic and pneumococcic, were likewise about equally distributed among the several types. It should be mentioned, however, that in all the cases of streptococcic sepsis necrotic lesions were found, though in one instance (Case 5, see protocol) they were focal in distribution.

In general it may be stated that the only constant etiological factor in cases of hemorrhagic necrosis is a severe circulatory disturbance. This statement is based on a careful review of clinical and autopsy findings in our large series of cases. The cause of the circulatory disturbance was in every case very evident. The majority showed advanced cardiac valvular disease, involving usually several valves. A few showed extreme myocardial fibrosis. The most extensive destruction of liver tissue (Case 8, Fig. 5) was seen in a case of aortic aneurism with rupture into the superior vena cava, resulting in the most extreme disturbance in circulation.

Type V. Collapse Fibrosis; So-Called "Cardiac Cirrhosis" (16 cases, or 14 per cent of the total number).—In this type of lesion each central vein is surrounded by a loose non-cellular connective tissue in which a quantity of blood pigment is found (Figs. 6 and 7). We have observed this lesion only in chronic cardiac cases, the majority of long standing, with a history of periodic attacks of decompensation, followed by improvement (Cases 11 and 12).

It is evident that the liver cells must have disappeared either by a process of atrophy or of necrosis. The presence of much free and intracellular blood pigment, and the demonstration in many sections of transitions from Type IV, have led us to conclude that collapse fibrosis represents usually the terminal stage of central hemorrhagic necrosis, as Mallory has suggested. The connective tissue, in most cases at least, seems to be merely a condensation of the pre-existing fibrillar connective-tissue framework in the affected portion of the lobule. Herxheimer, however, in a recent paper, has concluded that the reticular fibers (Gitterfasern) are considerably increased in advanced stasis, but his descriptions and illustrations are not altogether convincing. He does not appear to have taken into consideration the collapsed state of the lobule which follows extensive central necrosis. Two of our 16 cases (less than 2 per cent of the 112 cases of chronic passive congestion) seem to show an active proliferation of connective tissue (Case 11, see protocol). The change is not diffuse, being most pronounced at the surface of the organ. The microscopic picture is strikingly different from that of Laennec cirrhosis, in that the connective-tissue increase is confined to the region about the center of the lobule. In some places the central veins are connected by connective-tissue strands, encapsulated lobules of liver parenchyma being thus formed of which the bile ducts are the centers. In no case did we find evidence of cirrhosis of the ordinary nodular type developing as the result of chronic passive congestion. In rare cases, when the two lesions were seen in the same liver, the cirrhosis was obviously primary.

CONCLUSIONS.

1. The microscopic picture of the liver in chronic passive congestion is very varied. At least five types of lesion may be recognized:

(a) Capillary dilatation with atrophy of the cells toward the center of the lobule (Fig. 1); (b) central degeneration with or without capillary dilatation (Fig. 2); (c) marked fat accumulation in the cells about the hepatic veins with midzonal hyperemia (Fig. 3); (d) central necrosis with hemorrhage (Figs. 4 and 5); (e) collapse fibrosis (Figs. 6 and 7).

2. The type of lesion present at autopsy is determined chiefly by the degree of circulatory disturbance and its duration. Long-continued stasis of slight or moderate grade leads to capillary dilatation with progressive atrophy of the liver cells (Type I). Degenerative changes in the liver cells (Type II) are due either to stasis of more marked degree, or to moderate congestion in conjunction with infection. Extreme stasis results in central necrosis with hemorrhage (Type IV), which passes over into collapse fibrosis (Type V) if death be

delayed long enough. The latter lesion also results occasionally from an extreme degree of atrophy (Type I). Central fat accumulation with hyperemia of the intermediate zone is commonly associated with chronic rheumatic endocarditis in young individuals.

3. The necrosis of the liver cells in chronic passive congestion is the effect of stasis alone, leading to asphyxia of the cells farthest removed from their arterial blood supply. Infection plays a minor part in causing a definite necrosis, although it probably contributes to the production of degenerative changes in the liver cells (Type II). Very extensive necrosis is not infrequently seen in cases of extreme stasis unassociated with infection.

4. Active regeneration of liver tissue is not regularly seen in chronic passive congestion. It is conspicuously absent in those cases of hemorrhagic necrosis where the loss of liver tissue is greatest. It is observed most often in cases of circulatory disturbance of long standing.

5. Chronic passive congestion never leads to the development of cirrhosis of the usual portal or nodular type. Collapse fibrosis, not infrequently seen, is not a true cirrhosis, but a condensation of the reticular fibers where the liver cells have disappeared. In only 2 out of 112 cases of chronic passive congestion was an active new growth of connective tissue observed. In these the change was limited to certain parts of the liver, with an involvement of the central portion of the lobule only, producing a picture very different from that of portal cirrhosis.

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PROTOCOLS.

Type I.

Case 1.—Male, aged 46. Hay fever and asthma 13 years, digestive disturbances 2 years. Later symptoms: nocturnal dyspnœa, headache, weakness, œdema of legs and face. Treated in the hospital 7 weeks, where he developed furunculosis and staphylococcus bacteriæmia.

Anatomical Diagnosis.—Arteriosclerosis of smaller vessels; arteriosclerotic contracted kidney; emphysema; hypertrophy and dilatation of heart (weight, 710 gm.); staphylococcus abscesses in lungs and kidneys; bronchopneumonia; chronic passive congestion of organs.

Liver.—Enlarged, mottled, uniform distinct lobulation. *Micros.*—Moderate capillary dilatation, with atrophy of liver cells of inner half of lobule. No necrosis, and no degenerative changes except cloudy swelling.

Case 2.—Male, aged 58. The chief symptoms were weakness, dyspnœa, swelling of the feet and legs, cough. In hospital 4 days.

Anatomical Diagnosis.—Generalized arteriosclerosis, with involvement of coronaries; myocardial fibrosis; arteriosclerotic atrophy of kidneys (moderate); hypertrophy of heart (weight, 540 gm.); bilateral hydrothorax; chronic passive congestion of viscera.

Liver.—Enlarged, mottled, distinct lobulation. *Micros.*—Extreme capillary dilatation, with atrophy of liver cells near the hepatic veins.

Case 3.—Male, aged 59. Dyspnœa on exertion; orthopnœa; polyuria. In hospital three times during the last year of life; improved at first by rest in bed; during the last admission the œdema became very marked.

Anatomical Diagnosis.—Chronic nephritis (combined arteriosclerotic and inflammatory); hypertrophy and dilatation of heart (weight, 850 gm.); œdema of lungs; bilateral hydrothorax; chronic pancreatitis; chronic passive congestion of viscera.

Liver.—Typical "nutmeg" type; much blood flowed out when the vessels were cut. *Micros.* (Fig. 1).—Extreme capillary dilatation; atrophy of liver cells of the inner two-thirds of lobule.

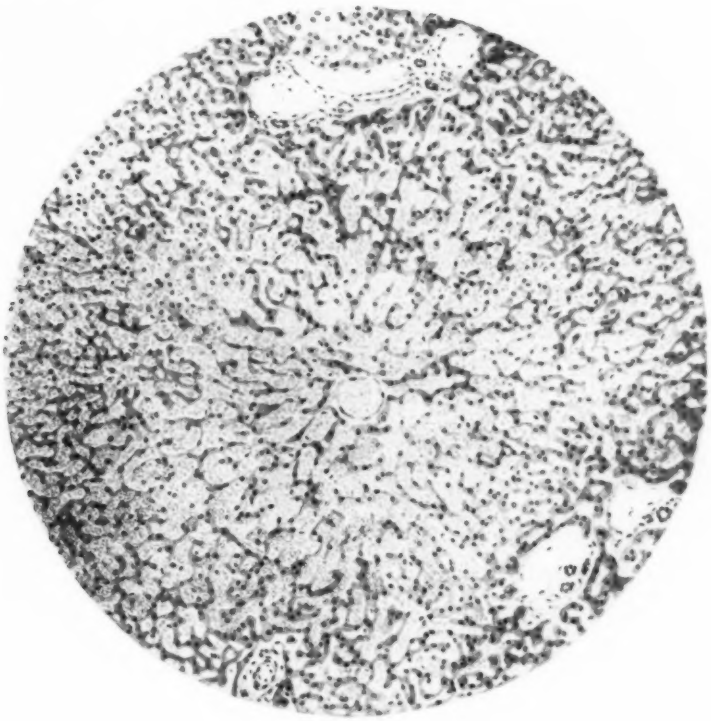
Type II.

Case 4.—Male, aged 42. Rheumatism 14 years ago; chief symptoms, precordial pain upon exertion and poor appetite. In hospital 1 day. Corrigan and capillary pulse; rapid respiration; chill; temperature 102.6° F.

Anatomical Diagnosis.—Syphilitic aortitis; aortic stenosis; hypertrophy of left ventricle (slight); focal degeneration of heart muscle; emphysema; acute fibrino-purulent pericarditis; chronic passive congestion of organs.

Liver.—Weight 2100 gm. Uniform distinct lobulation; periphery of lobule yellowish brown, center red and slightly sunken. *Micros.*—Cells in central half of lobule are reduced in size, cytoplasm vacuolated; nuclei well preserved; slight dilatation of capillaries. Peripheral cells show cloudy swelling.

Case 5.—Female, aged 36. Rheumatic fever many years ago; weakness, dyspnœa on exertion 4 years; swelling of legs, several



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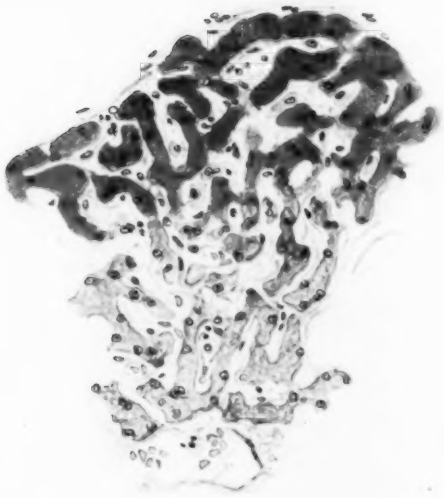
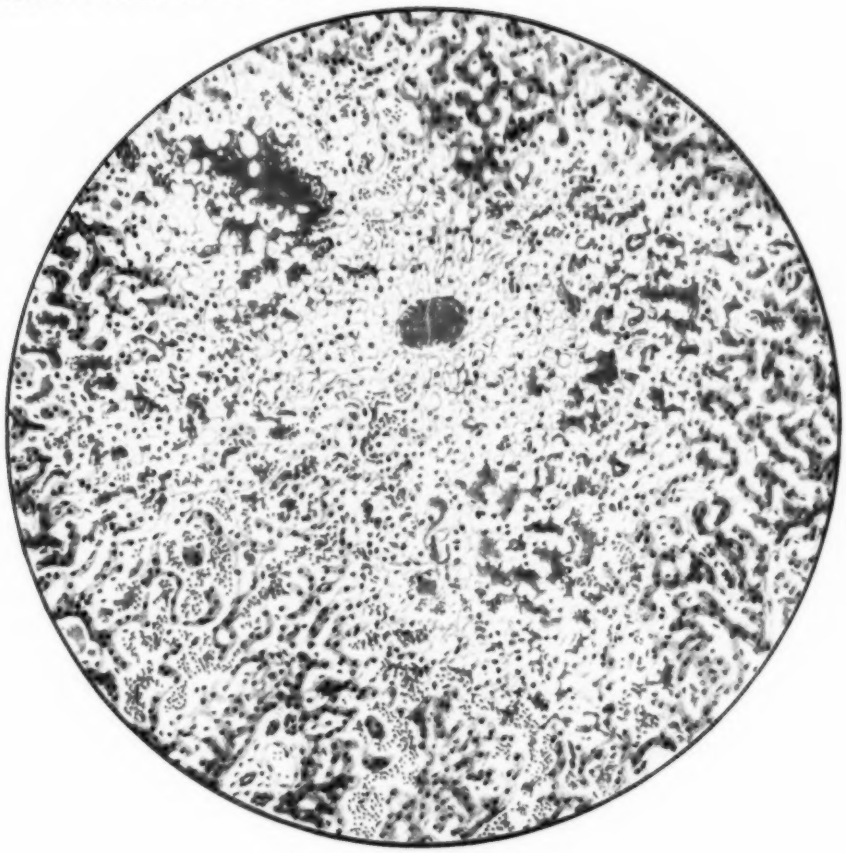


FIG. 2.



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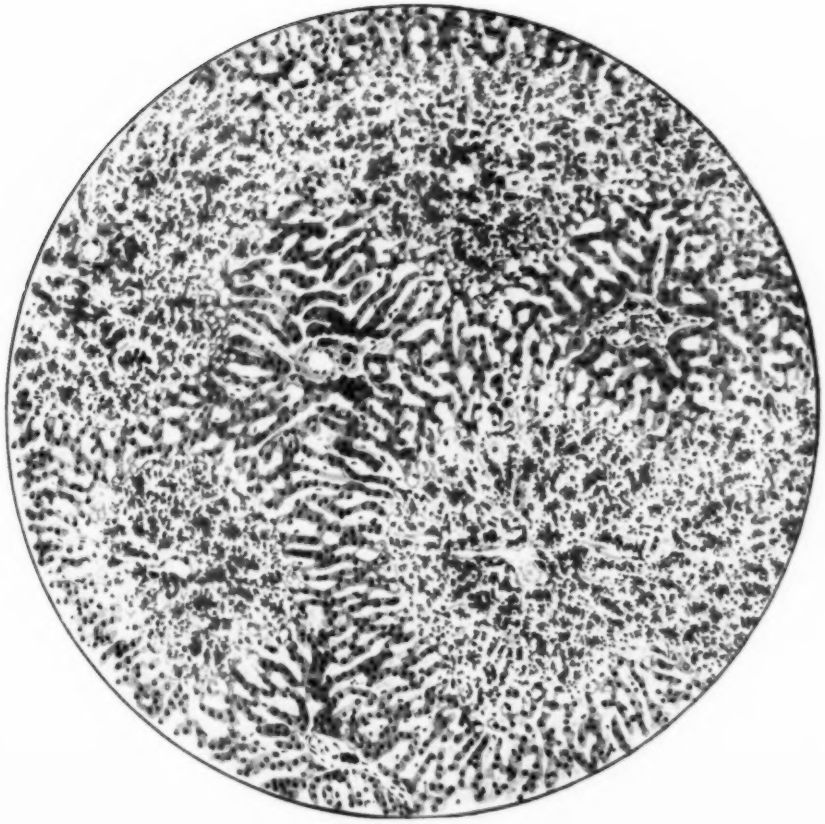

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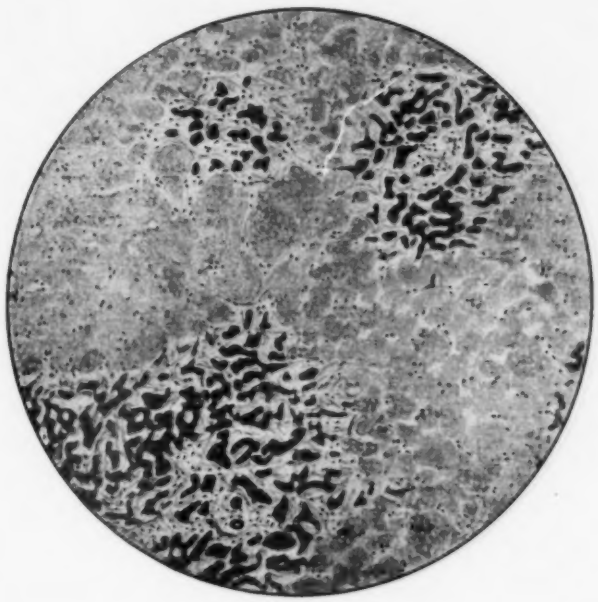

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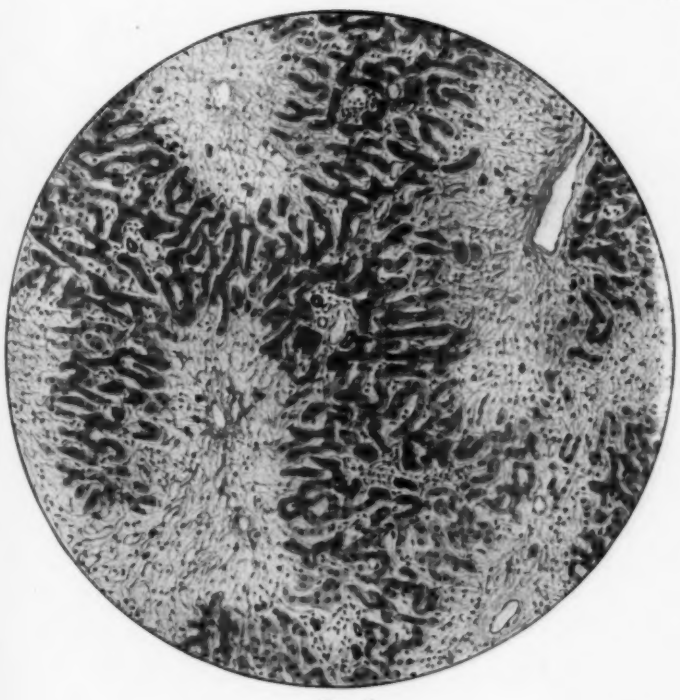

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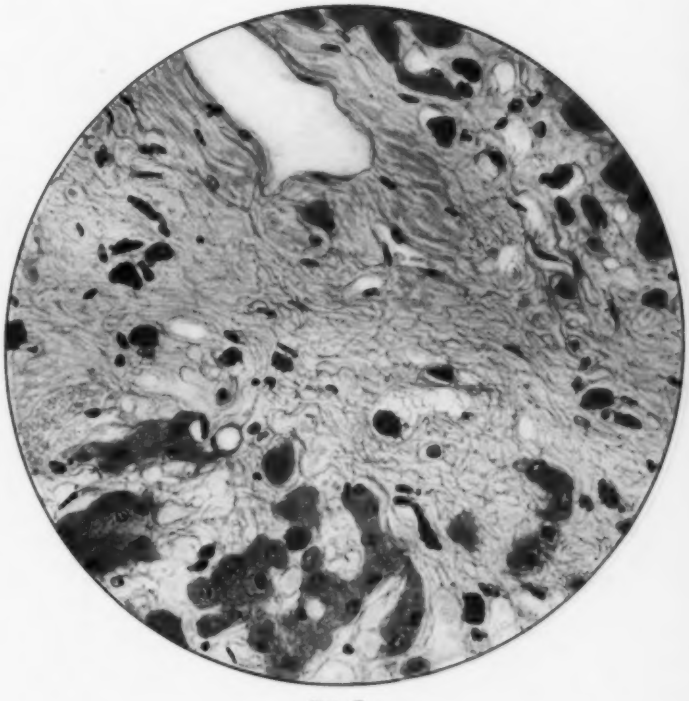

FIG. 7.

months. In hospital 6 weeks with chilly sensations, fever, weakness. *Streptococcus viridans* obtained in blood culture during life; circulatory disturbance not so pronounced as toxæmia.

Anatomical Diagnosis.—Acute and chronic endocarditis, involving mitral, aortic and tricuspid valves, and with vegetations on wall of auricle; acute myocarditis; hypertrophy of heart (weight, 580 gm.); œdema of lungs and extremities; acute and chronic glomerular nephritis; infarcts of kidneys; petechiæ in skin and mucous membranes; chronic passive congestion of organs.

Liver.—Weight, 1650 gm. Lobules small; uniform size, depressed red centers. *Micros.* (Fig. 2).—Cells in central half of lobule small, vacuolated and pigmented; vessels not dilated; occasional focal hemorrhages in mid-zonal portion of lobule.

Type III.

CASE 6.—Male, aged 10. Rheumatic fever 5 months ago, followed by swelling of ankles. In hospital 1 month. Described as typical heart case, with increasing œdema. Temperature normal, rising to 100° F. once.

Anatomical Diagnosis.—Chronic endocarditis, mitral and aortic; hypertrophy and dilatation of heart (weight, 270 gm.); chronic myocarditis; hydrothorax and ascites; petechiæ in skin.

Liver.—Somewhat enlarged; centers of lobules bright yellow, with central veins visible as small red points; a deep red ring surrounds the yellow; in places the red areas are extensive. *Micros.* (Fig. 3).—Marked fat accumulation in central cells; mid-zonal hyperæmia with necrosis in places.

CASE 7.—Male, aged 17. Acute rheumatic fever 7½ months before death, followed by dyspnœa, cyanosis and weakness. In hospital 7 months, where he developed a suppurative pleurisy, with intermittent fever, leucocytosis and cough.

Anatomical Diagnosis.—Chronic rheumatic endocarditis, mitral and aortic; acute rheumatic myocarditis; hypertrophy of heart (weight, 700 gm.); adherent pericardium; suppurative pleurisy; chronic pulmonary tuberculosis; chronic passive congestion of organs.

Liver.—Weight, 1200 gm. Irregularly mottled; central vein surrounded by yellow zone; red streaks and patches between center and periphery. *Micros.*—Few normal liver cells about portal spaces, central cells very fatty; mid-zonal hyperæmia.

Type IV.

CASE 8.—Female, aged 33. Shortness of breath 2½ years; cyanosis; difficulty in swallowing; swelling of face and neck 6 months. In hospital 14 times during the last year of life. Chief symptoms referable to pressure of aortic aneurism and extreme disturbance in circulation; never septic.

Anatomical Diagnosis.—Aneurism of ascending aorta perforating superior vena cava; aortic stenosis; fibrino-purulent pleurisy; jaundice; exreme circulatory stasis, most marked in liver.

Liver.—Weight, 1850 gm. Purplish red in color, with only small islands of yellowish-grey parenchyma surrounding the portal vessels. *Micros.* (Fig. 5).—Extreme hemorrhagic necrosis affecting the entire lobule in places.

CASE 9.—Male, aged 44. Periodic attacks of dyspnœa and faintness 18 years. One week before death he was seized with a sudden severe pain in the precordium, becoming intermittent in character. In the hospital he showed marked cyanosis; air hunger; tenderness in the epigastrium; enlarged liver.

Anatomical Diagnosis.—Generalized arteriosclerosis, involving the coronaries; thrombosis of the descending branch of the left coronary artery with infarction of the left ventricular wall; thrombi in the left ventricle and auricle; acute fibrinous pericarditis; arteriosclerotic atrophy of the kidney (slight); hypertrophy of the heart (weight, 675 gm.); chronic passive congestion of organs.

Liver.—Weight, 1510 gm. Firm, nutmeg color; centers of lobules deep red, depressed. *Micros.*—Recent necrosis of liver cells in the central two-thirds of the lobule; cell form preserved in most places, pyknosis and fragmentation of nuclei; beginning hemorrhage into the trabecular spaces in places.

CASE 10.—Male, aged 23. Acute rheumatism 3 years before death. Swelling of feet and abdomen 3 months; cough, orthopnœa, cyanosis. In hospital 6 weeks; pitting œdema of legs, ascites; pulsating liver. Temperature normal except 1 day. Leucocytes 10,300; polynuclears, 70 per cent; blood pressure, 104/72.

Anatomical Diagnosis.—Chronic rheumatic endocarditis and acute vegetative endocarditis, involving mitral, aortic and tricuspid valves; adherent pericardium; calcification of heart muscle (focal, microscopic); calcification of diaphragm; hypertrophy of heart (weight, 850 gm.); œdema of lungs; ascites; chronic passive congestion of viscera.

Liver.—Weight, 2000 gm. Strikingly mottled; light yellow areas along afferent blood-vessels on a bluish red background. *Micros.* (Fig. 4).—The inner half to three-fourths of each lobule shows a mass of blood with no surviving liver cells, surrounded by a narrow zone of fatty liver cells. Peripheral cells, normal.

Type V.

CASE 11.—Male, aged 45. In the hospital twice suffering from dyspnœa on exertion, nausea, vomiting, gnawing abdominal pain; excessive phlegm in throat; enlarged heart and liver; hemorrhoids.

Anatomical Diagnosis.—Myocardial fibrosis with arteriosclerosis of the coronary vessels; hypertrophy and dilatation of the heart (weight, 580 gm.); infarcts in the lung; thrombi in the heart; lobular pneumonia; abscesses in the lung; chronic passive congestion of organs.

Liver.—Weight, 1470 gm. Very firm and tough; distinct lobulation, centers of lobules depressed; peripheries pale. *Micros.*—Zone of actively proliferating connective tissue around each central vein; change found chiefly near surface of liver.

CASE 12.—Male, aged 55. Chief symptoms, dyspnœa, orthopnœa, swelling of abdomen and legs, scanty urine, 7 months' duration. In the hospital 7 weeks. Liver enlarged, tender and pulsating; frequent tappings of right chest; no history of infection.

Anatomical Diagnosis.—Arteriosclerosis of coronaries; myocardial fibrosis; hypertrophy and dilatation of heart (weight, 575 gm.); thrombi in auricles and ventricles; lobular pneumonia; œdema of lungs; hydrothorax; chronic passive congestion of organs.

Liver.—Weight, 1400 gm. Distinct lobulation; border of lobule elevated, intralobular tissue red and sunken. *Micros.* (Figs. 6 and 7).—Collapsed areas about central veins, deposition of much pigment. In some lobules typical hemorrhagic necrosis, and transitions into "collapse fibrosis."

ILLUSTRATIONS.

Fig. 1.—Chronic passive congestion, Type I. Marked dilatation of capillaries, especially in central zone; extreme atrophy of liver cells; no necrosis or hemorrhage. Case of nephritis, cardiac hypertrophy and dilatation. (See protocol, Case 3.)

Fig. 2.—Chronic passive congestion, Type II. Degenerative changes in cells of inner half of lobule. Affected cells are reduced in size; nuclei normal; cytoplasm vacuolated and pink-staining. No necrosis. Case of subacute bacterial and chronic endocarditis of mitral and aortic valves. (See protocol, Case 5.)

Fig. 3.—Chronic passive congestion, Type III. Cells about hepatic vein, very fatty; dilatation of capillaries in intermediate zone with focal hemorrhages. Case of chronic rheumatic endocarditis of mitral and aortic valves. (See protocol, Case 6.)

Fig. 4.—Chronic passive congestion, Type IV. Necrosis of cells in inner half of lobule with hemorrhage into the trabecular spaces.

Narrow zone of fatty cells surrounding necrotic areas. Peripheral cells normal. Case of chronic rheumatic endocarditis involving mitral, tricuspid and aortic valves. (See protocol, Case 10.)

Fig. 5.—Chronic passive congestion, Type IV. Extensive central necrosis with hemorrhage involving entire lobule in places. Case of aortic aneurism perforating superior vena cava. Extreme circulatory disturbance. (See protocol, Case 8.)

Fig. 6.—Chronic passive congestion, Type V. Disappearance of liver cells in central portion of lobule with collapse fibrosis and pigment deposition. No active proliferation of connective tissue. Peripheral cells are large and some show two nuclei. Case of arteriosclerosis of coronary vessels with advanced myocardial fibrosis. (See protocol, Case 12.)

Fig. 7.—Chronic passive congestion, Type V. Higher magnification of Fig. 6, showing condensation of reticulum about hepatic veins and phagocytosis of pigment by endothelial cells.

THE REACTION OF THE SPLEEN IN ACUTE INFECTIONS.

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The reactions of the spleen in the commoner acute infections merit more attention than that given them by the simple designation, acute splenic tumor. A complete understanding of the processes would go far in clearing up the obscure functions of the spleen, would do much in demonstrating the pathological physiology of many wandering cells of the body, and possibly point the way to a clearer appreciation of several pathological processes. But such an understanding is dependent upon a knowledge of the histology of the spleen and the various cells found there, and such knowledge of this as is available is not complete or definitely proven. But some points are known, and others have been suggested, and acute splenic tumor studied in the light of these establishes some of the suggestions made, and at least indicates a possible answer to some of the above questions. It has been the object of this study to interpret the histology of acute splenic tumor, as seen at autopsy, on the basis of what is already known of the cells in the spleen, and to control these interpretations by experimentally induced acute splenic tumor in animals under various conditions.

THE HISTOLOGY OF THE SPLEEN.

It here becomes necessary to discuss briefly what is known, and what has further been suggested, in regard to the histology of the spleen. The structure of the spleen as worked out by Weidenreich [1] and Mollier [2] will not be discussed in detail, as it is readily available in the original articles of these authors, and in various text-books of histology and pathology. It will suffice to restate from these authors that the Malpighian corpuscles are collars of lymphoid tissue around the arterioles of the spleen, arterioles that eventually empty into a wide network of venules in the pulp lined with endothelial cells; and between these venules, and for the most part passing freely in and out of them, lie cells of diverse form—the pulp cells. The Malpighian corpuscles can be considered as lymphoid nodules and, except for the occasional enlargement and proliferation of some of the large cells in the center,[3] seen in acute infections, especially in children (in all probability merely part of a general hyperplasia of the lymphopoietic tissue of the body), take no part in the processes resulting in acute splenic tumor. The pulp cells, however, are intimately concerned in the histological picture of acute splenic tumor, and demand further inquiry into their nature and function.

There has been much speculation but little proven about the different forms of mononuclear cells in the splenic pulp, and, although it can be stated with some degree of certainty that there are several definitely established types of cells present, a differentiation between all of them with the usual stains is not possible in tissue sections. True small lymphocytes may be recognized in any preparation, vitally staining histogenous macrophages are demonstrable by the vital stains, and myeloid cells are proven by the oxydase reaction. Yet there are still other cells for which definite diagnostic criteria are not available. Some of these pulp cells are intimately related to the reticular elements, others seem to be entirely independent of them; and in most routine tissue sections many cells that appear to be in the pulp probably in reality represent endothelium lining venous sinuses. And the mere recognition of endothelial cells as such would not end the problem as far as they are concerned; for they take an active part in the pathologic histology of acute splenic tumor, and are intimately related in some obscure manner to other mononuclear cells of the pulp. They can, for instance, become swollen and act as phagocytes, and their intimate relation, and perhaps transition, to the reticulum cells suggest that they may become free, wandering together with the other pulp cells. Mallory [4] recognized the phagocytic properties of these endothelial cells in typhoid fever, and was so convinced that they become free and subserve functions other than that of lining venous sinuses, that he speaks of many mononuclear wandering cells of the tissues and blood as endothelial leucocytes.[5] Marchand [6] likewise maintains they can become free, go over into the blood and become large mononuclear wandering cells; and the pathological picture in Gaucher's disease,[7] in which these cells, or closely related forms, are concerned in the pathological process with vitally staining reticulum cells,[8] makes it certain that the endothelium lining venous sinuses in the spleen must receive more attention in the histological study of acute splenic tumor than would be accorded them as mere lining pavement cells. The cells mentioned above with which the sinus endothelium appears so closely related, the so-called reticulo-endothelial cells—vitally staining histogenous macro-

phages—make up a widely distributed group of cells in the body with fairly well defined function and diverse morphology.[9] These are the principal cells concerned in the phagocytosis in typhoid fever noted by Mallory and named by him endothelial leucocytes, and in the pathological picture of Gaucher's disease.[8] Only after previous careful study with the vital stains can they be recognized on morphological grounds alone in the spleen by the usual stains, and then with no great certainty; but in vitally stained animals they can be demonstrated throughout the pulp and in the Malpighian corpuscles in intimate association with the reticulum.* The relation of these cells to other wandering cells of the body is obscure, but that they are active wandering cells is admitted by all observers, and some maintain they are intimately concerned with the mononuclear wandering cells of the blood.[5, 6, 10] Pappenheim,[11] although admitting such a relation for cells of this group elsewhere in the body, maintains that those in the spleen—which he names splenocytes—are fixed cells. Whatever their genetic relation may be, by means of the vital stain and oxydase reaction they can be differentiated from adult lymphoid and myeloid cells,[12] and study of their reaction in acute splenic tumors brings further proof that such a differentiation is justifiable. That, aside from the polymorphonuclear cells of the circulating blood present, myeloid or at least myelopotent cells are found in the spleen pulp seems likely from the myeloid metaplasia seen there under some conditions, and can be beautifully demonstrated by means of the oxydase reaction in frozen sections of the spleen.[13] By this method perhaps one-third or more of the cells of the pulp are seen to be myeloid, and the follicles to be entirely free of them. Of course many adult polymorphonuclear and oxydase mononuclear (so-called transitional) cells are present in the blood of the venous sinuses and pulp, but these do not account for all the oxydase cells seen there, and force one to the conclusion, in agreement with Paramusoff,[14] that even in the normal spleen there are certain mononuclear myelopotent immature cells that do not go over into the circulating blood. In addition to the readily recognized true lymphocytes, the vitally staining histogenous and the sinus endothelial cells, and the oxydase cells, there are yet others in the splenic pulp that morphologically cannot be distinguished from some of the cells identified as above outlined, but which react differently to these biological reactions. They are probably lymphoid in relation and many may be some type of plasma cell;[15, 16] and it seems certain that many of them are examples of the non-oxydase mononuclear cells of the blood, not filtered out there as Pappenheim would have it,[17] but formed in the spleen and by it contributed to the large mononuclear group of blood cells.[18] Furthermore, it would seem that the spleen is a more or less active erythropoietic organ,[18, 19, 20] so that it cannot be denied that some of these cells are fixed mother-cells of the erythrocytes, although the rare occurrence of normoblasts in the spleen normally makes this hard to believe. However, whatever the remote relations existing between cells of the splenic pulp are, it may be definitely stated that, with the exception of its vitally staining histogenous macrophages—and the endothelial cells—they are fundamentally hæmatopoietic in character. As part of the evidence in favor of this statement may here be cited the reaction of the splenic pulp to benzol poisoning. After sufficiently prolonged benzol administration the leucopoietic tissue is destroyed and the bone-marrow rendered aplastic. The splenic pulp is affected in the same manner as the bone-marrow, so that in heavily poisoned animals the spleen is represented by a collapsed bit of tissue made up only of reticulum, reticulum cells and endothelium.[21] And it may further be stated that the splenic pulp cells can be divided, on biological grounds, into three groups:[12, 22] (1) Vitally staining and sinus endothelial cells; (2) oxydase-containing cells; (3) non-oxydase mononuclear cells and true lymphocytes. It is on the basis of this classification that acute splenic tumor has been studied.

* It seems evident that the Malpighian corpuscles are merely lymphoid nodules, and that most of the large cells at the center are immature fixed cells that give rise to the true small lymphocytes. The presence also of a few vitally staining histogenous macrophages as reticulum cells in the same areas, and the different functional activity which they manifest under some conditions, probably have given rise to most of the scepticism in regard to the lymphoblastic character of most of the large fixed cells in the center of the follicles.

STUDY OF AUTOPSY MATERIAL.

In the gross, two types of acute splenic tumor may be recognized which, from their most obvious characteristic, will here be spoken of as red and gray, a designation already in common

RED.	GRAY.
TYPHOID AND PARATYPHOID FEVER, ETC.	PNEUMONIA, SEPTICEMIA, ENDOCARDITIS, ETC.
The largest acute splenic tumors are of this type. They may, however, be quite small. Those studied varied in weight from 120 to 950 gm., with an average for 21 specimens of 387 gm.	The spleen may be very large, but the increase in size is commonly only moderate. Those studied varied in weight from 100 to 750 gm., with an average for 29 specimens of 324 gm.
The organ is very soft and diffluent; it does not maintain its shape.	It is soft but not diffluent as in the red type; the organ maintains its shape.
The capsule is always tense.	The capsule is never wrinkled, but is often not tense.
The pulp bulges markedly above the level of the cut surface, and is very moist.	The pulp bulges moderately above the level of the cut surface, and is not so moist as in the red type.
Dark red-brown color, homogeneous.	Dirty red-gray color; often mottled dark-red and gray.
The trabeculæ are completely obscured; they become very prominent after the cut surface has been scraped.	The trabeculæ are not completely obscured, and occasionally seem more prominent than usual. They do not become so much more prominent, as in the red type when the cut surface is scraped.
The spleen may collapse markedly after section of the vessels.	The spleen shows practically no collapse after section of the vessels.

use. All acute splenic tumors studied have been found to belong to one or the other of these two types, and only very rarely is an example encountered which cannot readily be placed in its proper group on gross inspection alone. Named from the most easily appreciated difference, these two types of acute splenic tumor have other individual characteristics that are very constant in occurrence, those of the red practically never seen in the gray, and *vice versa*. Similarly, their clinical association is just as constant, the red, and only the red type, seen in typhoid fever and typhoid group infections, and practically in no other condition; the gray, and always the gray type, wider in its distribution, occurring in pneumonia, bacterial endocarditis and other staphylococcus and streptococcus infections, etc. The gross differences between these two kinds of acute splenic tumor may be conveniently brought out by tabulation as shown on the preceding page.

Under the microscope there are similarly two characteristic pictures in acute splenic tumor, the line of division running parallel to that of the classification based on gross appearances. Some sections are encountered that are not typical of either, and present difficulties in the interpretation of the histological picture; but most of them can be properly placed without hesitation.

1. *Red Acute Splenic Tumor* (Fig. 1).—For a description of the histology of this type of acute splenic tumor little can be added to that of Mallory for the changes in the spleen in typhoid fever:[4]

> As a rule the lymph nodules of the spleen do not show any marked change in typhoid fever. In certain cases, however, some or all of the nodules show to a greater or less extent the same formation of phagocytic cells from the endothelial cells of the reticulum that is found in the lymphoid tissue of the intestine.
>
> The most marked changes of the spleen are those found in the blood-vessels and spaces of the pulp. They are much dilated and filled with large phagocytic cells containing principally red blood globules usually in very large numbers, but also lymphoid and plasma cells and polymorphonuclear leucocytes. These phagocytic cells are derived chiefly or entirely by proliferation and desquamation from the endothelial cells lining the vessels. Occasionally mitosis takes place in the cells lying free in the blood. Sometimes the blood-vessels and spaces become occluded by masses of these large cells, which degenerate and become bound together by a meshwork of fibrin.
>
> Besides this general proliferative process we get, as in the intestine, numerous plasma cells in the veins and in the splenic pulp. Many of them show amœboid shapes and not infrequently mitosis. In some of the splenic veins, especially the larger ones, the lining endothelium is lifted up by masses of large phagocytic cells, and of lymphoid and plasma cells. In places these cells degenerate and fibrin forms between and around them.

The great amount of blood in the sinuses and pulp and the striking proliferation of the reticular and endothelial cells mentioned by Mallory are to be observed as the two most characteristic features of this type of acute splenic tumor. The great scarcity and almost complete absence in many sections of polymorphonuclear cells and the diminution of pulp cells of all types, should be emphasized. That some mononuclear cells of special morphology, considered by Mallory to be plasma cells, are present in increased numbers must be admitted. Although we realize that no definite statement of their true character is possible, their intimate relation with the reticular and endothelial elements, which might even be interpreted as proliferation from them, makes it seem possible that many are in reality changed forms of endothelial cells or the vitally staining histogenous macrophages. The group of vitally staining cells includes some showing diverse morphological characteristics,[9] and some have many points of resemblance to true plasma cells.[12]

2. *Gray Acute Splenic Tumor* (Fig. 2).—In contradistinction to the red type, the gray acute splenic tumor is characterized by the cellularity of the tissue; and although an excess of blood is present, it is for the most part confined to the venous sinuses. The endothelial cells lining the venous sinuses are little, if at all, swollen and never show proliferation. The cells of the reticulum are often somewhat swollen, but are not increased in number, and show practically no proliferation. One of these, containing red blood cells and tissue debris, is occasionally encountered, but phagocytosis is not common. The Malpighian corpuscles in some specimens are large, and in others small; but they never show any undue prominence of the large fixed cells at the center of the follicle, such as is to be observed in the red type, or fragmentation of the true small lymphocytes around the periphery. The cellularity of the sections is dependent on the number of cells in the pulp which are present in more than normal proportions in spite of the active congestion of the organ, manifested by the distention of the venous sinuses with blood. Many of these cells are polymorphonuclears, many have the morphological characteristics of normal oxydase mononuclears and myelocytes. Among the great numbers of pulp cells seen in gray acute splenic tumor, these cells are shown by the oxydase reaction to be more than proportionately increased, although this proportionate increase of the oxydase-containing cells is always slight and never striking. There are also a few nucleated red blood cells in each specimen, never numerous but always to be found if searched for diligently enough. The other cells are lymphocytes, which perhaps are increased in number but certainly not proportionately, and the obscure non-vital staining, non-oxydase mononuclear cells of the normal pulp mentioned above. The predominance of the cells resembling plasma cells, which commonly occurs in the red, is not seen in this type. In the gray type the trabeculæ seem to be stouter and more prominent than in the red acute splenic tumors.

Thus it is apparent from the study of acute splenic tumors as seen at autopsy, that there are two distinct types, each of which has certain distinctive characteristics and both an excess of blood, show in common active congestion. The size of the spleen is, entirely in the red and in large part in the gray acute splenic tumors, dependent upon the amount of congestion, sections from the larger spleens showing regularly more blood than those from the smaller. The softer consistence and red color of the red type are a result of the excess of blood present, the somewhat firmer consistence and gray color of the gray type are due to its smaller amount of blood and the

greater abundance of pulp cells. The red acute splenic tumors are characterized by a diminution in the pulp cells, particularly the myeloid elements, proliferation of the vitally staining reticulum and the endothelial macrophages, and an active phagocytosis; whereas in the gray type we have an increase in the pulp cells, especially the myeloid elements, absence of increase in the macrophages, and only a slight grade of phagocytosis. It is more than incidental that typhoid fever, a clinical condition associated with hypoleucocytosis and showing pathologically active phagocytosis with proliferation of the macrophages in the lymph glands, lymph follicles of the intestine, etc.,[4] together with a diminution of the leucopoietic function of the bone-marrow,[23] should show in the spleen the changes outlined above; and that those clinical conditions associated with a hyperleucocytosis, hyperactivity of the bone-marrow [23] and practically no phagocytosis, present the reaction in the spleen already described for them. On the basis of these studies it seems safe to postulate a relation between the reactions in the spleen in acute infections and their characteristic general manifestations; to say that, in addition to the active congestion present in each, the histological picture seen in the red type of acute splenic tumor is part of the general associated leucopoietic, especially myelopoietic, inhibition, with consequent hyperplasia of the histogenous macrophages; and that that of the gray type is part of a hyperplasia of the leucopoietic, especially the myelopoietic, tissues of the body related to the hyperleucocytosis present.

To afford experimental evidence for these hypotheses the following experiments were undertaken, in which an attempt was made to induce acute splenic tumor of both the red and the gray types in animals under various conditions.

EXPERIMENTAL PART.

TECHNIQUE.

Rabbits were used in all the experiments. Except for the presence of oxyphile with relative decrease in neutrophile polymorphonuclears, the cells in these animals are similar to those in the human subject. The histology of the rabbit spleen is essentially like that of the human spleen, except that the Malpighian corpuscles are relatively much larger, the venous sinuses stand out more prominently, and the pulp is relatively less abundant. The spleen of the rabbit seems to be very sensitive to infections, for animals suffering from no more severe infection than early "snuffles" regularly present some evidence of acute splenic tumor. Rabbits cannot be killed with strains of the human typhoid organisms, but with them reactions can be produced in the spleen without the animal even showing evidence of being ill. The most satisfactory reaction to organisms of this type, however, were obtained by the intravenous inoculation of 1/15 to 1/50 of a 24-hour agar slant culture of an organism isolated from an epidemic of rat typhoid, studied and identified by Pappenheimer [24] as identical with *B. enteritidis* (Gaertner). To produce gray acute splenic tumor pneumonia was induced by the intrabronchial inoculation after the method of Meltzer [25] of 8 cc. of a 24-hour neutral broth culture of several different stains of attenuated pneumococci and streptococci; and to produce a cellular pneumonic exudate without bacillary intoxication, 8 cc. of a 33 per cent solution of sterile egg-yolk in neutral broth, as used by Kline and Meltzer,[26] were similarly injected. To render animals aleukemic, benzol was administered subcutaneously, 1 cc. per kilogram of body weight in an equal amount of olive oil, as used by Selling.[21] In these benzol experiments most of the observations were made on animals not entirely aleukemic; for in such animals the resistance is so much lowered that inoculation with any pathogenic organism kills before pathological changes have had time to take place.

I. ACUTE SPLENIC TUMOR IN RABBITS.

These experimental acute splenic tumors, although induced by the same or closely related organisms that give rise on the one hand to the red and on the other to the gray type in human subjects, in rabbits cannot be divided into these two classes on the gross appearances alone. The difference in size encountered was considerable, depending, in large part it seems, on the duration of the pathological process, since the animals that were heavily inoculated and died early did not show as large tumors as those that received smaller doses and survived for a relatively long time. As in human acute splenic tumor, the size depended almost entirely on the amount of active congestion present. The spleen was always soft, rarely diffluent, and the edges markedly rounded. On section the pulp bulged far beyond the level of the cut, and much material could be scraped from the surface, although in none of these acute splenic tumors (of rabbits), however induced, was the spleen parenchyma as soft or as moist as in many human cases. In many of these acute splenic tumors, independently of the factor used to produce it, the pulp had a mottled appearance, due to the relatively enormous size of the Malpighian corpuscles which stood out as gray dots. Except for these, the pulp had a dark red-brown color, never the pronounced dirty gray seen in the human gray type. Some variations in color from brown to gray occurred, but the small expanse of surface presented for examination on section of the rabbit's spleen did not make possible a reliable differentiation on this characteristic alone.

The microscopical picture, however, was distinctive, permitting a division into two groups, one produced by organisms giving rise to red and the other by those causing gray acute splenic tumor in human beings. The histological picture of each type corresponded closely, after making allowances for the differences between the normal histology of the human and the rabbit spleen mentioned above, to the corresponding type of human acute splenic tumor.

1. *After Typhoid-Group Inoculation.*—None of these acute splenic tumors, examined at periods varying from three to seventy-two hours after inoculation, and independently of the dose employed, showed the active congestion seen in the corresponding human type, although in the older ones it was more marked than in the earlier. The same increase in prominence and activity of the reticular and endothelial elements was present, with perhaps evidence of phagocytosis

not as marked; and the same diminution of the other cells of the pulp was to be observed. The increase in plasma-cell forms was not so noticeable in rabbits as in human typhoid acute splenic tumors. In addition to these changes, there were large and numerous areas of necrosis, rarely seen in human acute splenic tumors and never to the same extent; and in these areas of necrosis there was regularly a deposit of fibrin, occasionally delicate, but more often dense and sometimes occurring in compact plugs.

2. *With Pneumonia Induced by Intrabronchial Pneumococcus and Streptococcus Inoculation.*—As was noted in those previously discussed, none of these acute splenic tumors, examined at periods varying from five to fifty-four hours after inoculation, showed an advanced grade of active congestion. They were, however, often as much congested as those induced by strains of typhoid organisms in rabbits killed at corresponding periods after inoculation (Fig. 3). None of them showed swelling or proliferation of the reticular or endothelial elements, and all, particularly those induced by intratracheal inoculation of streptococcus strains, presented evidence of hyperactivity of the other cells in the pulp, and especially the myeloid elements, as evidenced by the increased number of oxydase cells. No areas of necrosis were seen in the acute splenic tumors induced by these organisms. In contrast to the human gray acute splenic tumors, the plasma-cell forms were increased as much in this type as in the rabbit typhoid spleens.

II. ACUTE SPLENIC TUMOR ASSOCIATED WITH A STERILE PNEUMONIC EXUDATE.

Several animals were inoculated intrabronchially with a sterile 33 per cent solution of egg-yolk in neutral broth. Such a procedure gives rise to a cellular pneumonic exudate with a functional demand for cells and without any general bacterial intoxication. In the spleens of these animals, studied at periods varying from ten hours to four days, there was a mild grade of active congestion with some increase in size (Fig. 3) which, although much less than that seen in the spleens of the infected animals, could be interpreted from the gross as acute splenic tumor. Microscopical study revealed an increase in the pulp cells, as seen in the spleen accompanying the pneumonia induced by bacteria.

III. RED ACUTE SPLENIC TUMOR IN ALEUKEMIC ANIMALS.

To determine whether the characteristic histological details of red acute splenic tumor, interpreted as showing an inhibition of the leucopoietic tissue of the pulp and stimulation of the reticulo-endothelial elements, can occur in the absence of the hæmatopoietic cells of the spleen, animals were inoculated with typhoid cultures, as above outlined, after poisoning with benzol. All these spleens, although only slightly enlarged above the normal (Fig. 3), were larger than those of animals similarly poisoned with benzol. They were soft, and the pulp was moist and of a dark brick-red color. Under the microscope the venous sinuses were seen to be congested. Owing to the great diminution or complete absence of the other cells of the pulp and the resulting relative increase in the reticulum and endothelial cells seen in the spleen in benzolized animals, the interpretation of the splenic reaction in these animals after inoculation with typhoid cultures was difficult. The reticulum and the endothelial cells are, of course, prominent, much more so than in animals inoculated with typhoid cultures alone, or only poisoned with benzol. They are markedly swollen and show some evidence of proliferation. Phagocytosis, although not striking, is present. It is noteworthy that the plasma-cell forms, often seen abundantly in human red acute splenic tumor and in both types of acute splenic tumor in rabbits, are relatively scarce in these preparations.

IV. FAILURE TO PRODUCE GRAY ACUTE SPLENIC TUMOR IN ALEUKEMIC ANIMALS.

To determine if the histological changes characteristic of gray acute splenic tumor, interpreted as being entirely dependent on a stimulation of the leucopoietic cells of the pulp, can occur in the absence of the hematopoietic cells of the spleen, pneumonia was induced in animals rendered aleukemic by benzol administration. The inoculations were made on animals with white blood counts on the day previous to inoculation of 600 to 1900. With completely aleukemic animals the bacterial toxins kill too quickly to allow of the development of any splenic reaction. One animal, however, with a white blood cell count of 600 lived six hours after inoculation, long enough for the development of some acute splenic tumor in an animal not poisoned by benzol. The spleen of this animal showed no congestion, but exhibited the collapsed collection of endothelium and reticulum seen in completely benzolized animals (Fig. 3), without infection. Other animals with white blood cell counts less than 2000, similarly inoculated and autopsied after longer periods, showed only the changes in the spleen for animals thus poisoned, and practically no congestion.

V. CHANGES IN THE BONE-MARROW.

The study of the bone-marrow in these experiments was instructive. The myeloid hyperplasia of the bone-marrow in conditions showing the gray acute splenic tumor, and the necroses, myeloid aplasia and prominence of the reticular elements in those showing the red acute splenic tumor, have already been noted in human cases.[23] Similar observations were made on the bone-marrow of these rabbits with experimentally produced acute splenic tumor. In the typhoid animals the histological changes in the bone-marrow were identical with those in the spleen—aplasia of the myeloid elements, numerous and extensive necroses and swelling of the reticulum cells with some phagocytosis. In the pneumonia animals hyperplasia of the bone-marrow was to be observed, slight in some, advanced in other cases. In some, although not in all of these animals having acute splenic tumors, the bone-marrow was congested. The presence or absence of this congestion of the bone-marrow seemed to bear no relation to the substance used to induce the acute splenic tumor.

VI. BONE-MARROW CHANGES IN PNEUMONIA IN SPLENECTOMIZED ANIMALS.

After our studies on the character of the pneumonic exudate in the pneumonias mentioned, which has been reported elsewhere,[27] pneumonia was induced in animals that had been splenectomized from one hour to two and a half months previously, and the pneumonia exudate was studied at different periods for any quantitative or qualitative change. There was no change in the character of the cells in the exudate at any stage of the pneumonic process. The number of cells seemed to be diminished, but the great variation in this finding encountered in experimentally induced pneumonia in animals with their spleens intact, allows of no deductions from this observation. In these splenectomized animals, however, induced pneumonia was accompanied by more hyperplasia of the bone-marrow, as compared with the normal animals or the pneumonia animals that had not been splenectomized.

These experiments show that in rabbits two types of acute splenic tumor resembling closely the two human types can be induced by similar etiological agents. The primary characteristics are always the same as those of the corresponding human type induced by the same type of infection, except that, whereas a noticeable increase in the plasma-cell forms occurs only in the human red type, in the rabbits it is seen in both. A functional demand for leucocytes, even in the absence of a general bacterial intoxication, can produce changes in the splenic pulp qualitatively similar to those of gray acute splenic tumor, the only real difference being in the lesser degree of active congestion present. The characteristic histological features of red acute splenic tumor can appear after the destruction of the leucopoietic elements; but gray acute splenic tumor cannot be produced after the leucopoietic tissue has been destroyed. Almost identical changes occur in the bone-marrow as are seen in the pulp of the two types of acute splenic tumor; and the conditions that give rise to gray acute splenic tumor, when induced in splenectomized animals, result in greater hyperplasia of the bone-marrow than is present under similar conditions in animals with the spleen intact.

DISCUSSION.

Recognizing in the splenic pulp three great groups of cells [12, 22]—the reticulo-endothelial elements, the oxydase-containing myeloid and perhaps non-oxydase myelopotent cells, and a large residue of cells other than these above, including lymphoid cells of various types and stages of maturity, and probably undifferentiated erythropoietic cells, the reactions of the spleen in the commoner acute infections admit of enlightening analysis. This analysis indicates that the conditions included under the term *acute splenic tumor* embrace two major reactions, in effect almost opposites of each other. Both these reactions of the spleen are associated with an active congestion, as is to be expected in any tissue reaction, and the gross characteristics of the acute splenic tumor, the size, consistence, and in large part the color, are dependent upon the amount of congestion present. The type of reaction showing the greatest congestion, the red acute splenic tumor seen in typhoid fever and closely allied infections, is characterized by an inhibition of myelopoietic activity of the pulp, and hyperplasia and hyperactivity of the reticular and endothelial macrophages. That type of reaction regularly showing less congestion, the acute splenic tumor of pneumonia, endocarditis, and other staphylococcic and streptococcic infections, and others, regularly shows evidence of myelopoietic activety in the pulp, with slight hyperplasia of the other cells with the exception of the reticulo-endothelial elements.

One cannot, of course, say that only the reticular and endothelial cells are concerned in red acute splenic tumor, and that the other elements alone are active in the gray type. The phagocytic activities of the polymorphonuclear and lymphoid cells, as compared with the histogenous macrophages, for want of a more specific term designated reticulo-endothelial cells, must be recalled in this connection. The polymorphonuclears, and to a less extent the lymphocytes, are the active phagocytes, the first line of defense, exhibiting phagocytic activity during the first hour after the introduction of the foreign body.[12, 28] Later the more slowly moving histogenous macrophages take up the struggle, ingesting particulate matter either too large or too small for the polymorphonuclear cells,[12, 28] any other residue the polymorphonuclears have been unable to handle, and even dead polymorphonuclears loaded with debris that have succumbed in the struggle. In typhoid fever, no doubt, such a process occurs, so that in the early stages before the hematogenous elements have been injured by the toxin, if there is any phagocytosis to be carried on, much is accomplished by the polymorphonuclear cells. And even in the late stages of the disease an occasional phagocytic polymorphonuclear cell is encountered. But later, when the myelopoietic elements are crippled, as they are in typhoid fever, the burden of phagocytosis falls on the histogenous macrophages, those cells which uninjured by one myeloid toxin, benzol, are likewise uninfluenced by another, the toxin of typhoid fever. Owing to indefinite morphological characteristics, all phagocytic cells in the spleen cannot be definitely diagnosed as histogenous or hematogenous. But many can, throught their morphology and relations, be recognized as identical with the vitally staining and endothelial cells, and therefore identified as reticulo-endothelial cells. This is demonstrated more satisfactorily in the Peyer's patches of the intestine than in the spleen, for there phagocytosis, because of the greater amount of tissue debris, is more marked. In typhoid fever, although it cannot be said that only the histogenous macrophages are active, the characteristic histological picture seen not only in the spleen but also in the bone-marrow, lymph glands and follicles, is dependent on the phagocytosis exhibited by these cells.

Similarly, in gray acute splenic tumor, it is not the hematogenous cells alone that are active. On hypothetical grounds some phagocytosis of the histogenous elements is to be expected, and does occur. But because of the slight amount of tissue debris present in the spleen in these conditions, and because of the unimpeded activity of the hematogenous cells and even increase in number, the activities of the histogenous

cells are not conspicuous, and it is the hematogenous cells that have to do with the characteristic features of the histological picture in the gray acute splenic tumor.

It seems probable that the general bacterial intoxication has much to do in bringing about the reactions seen in the spleen. In infections giving rise to acute splenic tumor of the red type, the inhibition of the myelopoietic functions in the spleen and bone-marrow is probably entirely of toxic origin, but the increase of the reticulum and endothelial cells may be a functional hyperplasia. The stimulation of the myelopoietic functions of the splenic pulp and bone-marrow in conditions associated with gray acute splenic tumor is in large part a functional hyperplasia, as evidenced by the production of practically identical changes by a simple demand for cells without any bacterial infection. That such a functional demand for myeloid cells is responsible for the changes mentioned in gray acute splenic tumor seems evident from the fact that they do not appear when the myeloid tissue is destroyed by benzol, and that infections giving rise to gray acute splenic tumor, when induced in splenectomized animals, are accompanied by more than the usual bone-marrow hyperplasia. On the other hand, the characteristic histological changes of red acute splenic tumor are entirely independent of the myelopotent tissue, for they can occur after the destruction of this tissue by benzol. In accord with the statement of Jawein,[29] it may be said that the largest acute splenic tumors are those showing active phagocytosis, the red type of typhoid fever; but, in disagreement with him, it seems that this reaction is not dependent solely on destruction of red blood cells. And in the gray type, destruction of red blood cells, or phagocytosis of cellular debris, is not a factor at all in the production of the changes that occur. Although it cannot be denied from the results of this study that myeloid metaplasia of the spleen can result from anemia and blood destruction, it can be positively stated that the myeloid activity of the spleen in the gray acute splenic tumor of some infections is not so caused; but that it is rather a toxic stimulation, as Hertz[30] would have it, or more likely in large part a functional hyperplasia.

CONCLUSIONS.

Although this analysis of the histopathology of acute splenic tumor is based upon somewhat fragmentary knowledge of the cellular content of the spleen, it brings further proof that a separation of the vitally staining histogenous macrophages and the endothelial cells from the other cells of the mature organism is justified functionally, although not always possible on morphological grounds; and that the spleen is an integral part of the blood system of the body, responding quickly to any influence inhibiting or stimulating hematopoietic activity. And in regard to the reaction of the spleen in the commoner acute infections it may be said that:

(1) Acute splenic tumors all fall into one or two major groups; the red type, associated with typhoid fever and closely related infections, and the gray type, with pneumococcus, staphylococcus, streptococcus and other infections.

(2) The spleen in each type of acute splenic tumor shows active congestion upon the extent of which depends the size, consistence, and in large part the color of the organ.

(3) The histological picture of red acute splenic tumor is distinctively characterized by hyperplasia and activity, as evidenced by phagocytosis of the reticulo-endothelial macrophages and decrease in number of the other cells of the pulp; and these changes are dependent on a toxic inhibition of the leucopoietic functions of the body associated with typhoid fever, and a stimulation, perhaps functional, of the reticular and endothelial cells.

(4) The histological picture of gray acute splenic tumor is distinctively characterized by an increase in the pulp cells, especially the oxydase-containing myeloid elements, without any proliferation, or increased activity, of the reticular and endothelial cells; and these changes result for the most part from a functional demand for leucocytes.

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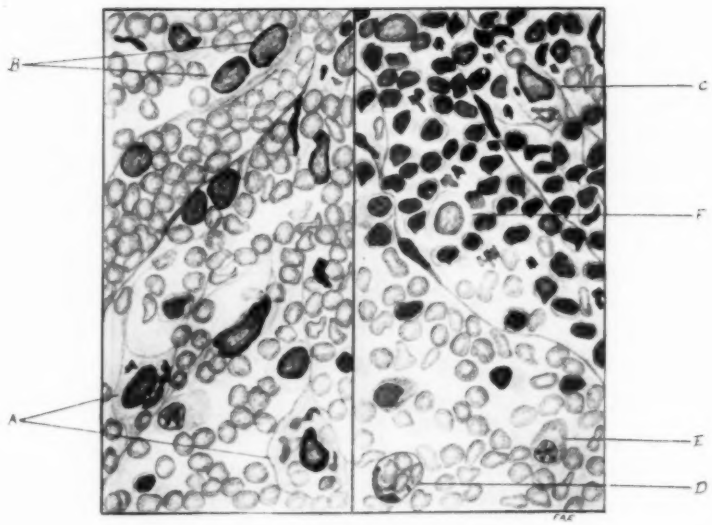

FIG. 1.

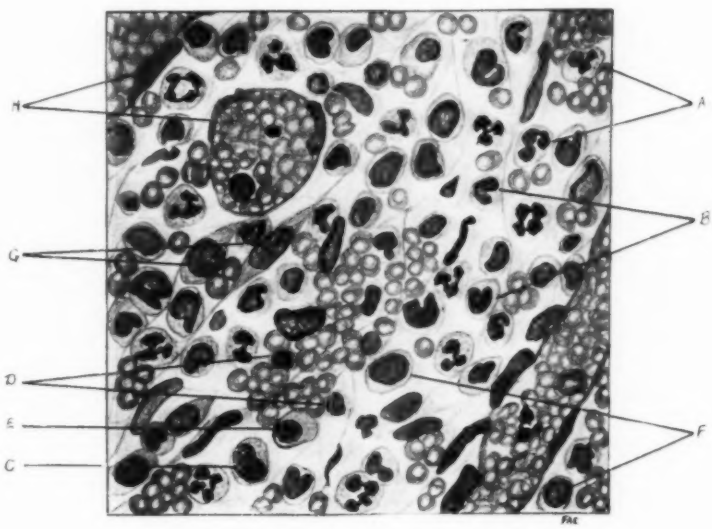

FIG. 2.

FIG. 3.

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DESCRIPTION OF FIGURES.

FIG. 1.—*Red Acute Splenic Tumor.*—The excess of blood present and diminution in the number of pulp cells is characteristic.

a. Phagocytic reticulum cells of the pulp.
b. Swollen endothelial cells of the pulp.
c. Phagocytic reticulum cell of the Malpighian corpuscle.
d. Phagocytic cell of the pulp apparently not related to the reticulum.
e. Plasma cell.
f. Lymphoblastic cell of the Malpighian corpuscle.

FIG. 2.—*Gray Acute Splenic Tumor.*—The mild congestion and cellularity of the pulp are noteworthy. The endothelium and reticulum cells are swollen, but there is no phagocytosis evident. Polymorphonuclear cells are numerous.

a. Polymorphonuclear cells.
b. Oxydase mononuclear cells.
c. Myelocyte.
d. Lymphocytes.
e. Plasma cell.
f. Non-oxydase mononuclear cells.
g. Reticulum cells.
h. Endothelial cells.

FIG. 3.—Cross-sections through the greatest diameter of rabbit spleens, showing acute splenic tumor, and illustrating the variations in size under different conditions. This, in effect, is only a record of the amount of active congestion present.

IRON IMPREGNATION AND INCRUSTATION OF VARIOUS TISSUES.

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The presence of iron in calcium deposits has recently had a new importance attached to it in the demonstration of curious bodies believed by some to be fungi. In the intensive researches that have been made upon the various tissues in pseudo-leukæmia, attempts have been repeatedly made to demonstrate micro-organisms as causative agents. Cultural and histological methods have been applied, and in some instances success has been claimed in demonstrating bacterial types. In part, at least, it would appear that the histological methods have been most uncertain, as the development of artefacts, as well as inorganic precipitates, have suggested conclusions which closer scrutiny cannot substantiate.

Recently Sprunt has called special attention to these fallacies. In 1911 he reported peculiar findings in a case of splenomegaly associated with liver cirrhosis. The diffusely fibrosed spleen contained "ocher-colored patches" which, on microscopical examination, showed a peculiar pigment about the trabeculæ and particularly about the blood-vessels. The vessels lay amidst masses of fibrosis, and in the vessel wall, as well as to a lesser extent in the surrounding tissues, were bands and threads of golden pigment. Sprunt was able to demonstrate calcium and iron in these deposits and found that they occurred mainly in elastic tissue. The elastic fibers had undergone various grades of degeneration which then appeared to have a chemical affinity for both calcium and iron. These impregnated salts were readily removed from the tissues with dilute mineral acids.

Subsequently Gibson reported the presence of a streptothrix in the spleens of six cases of "splenic anæmia." Four of these cases were of the variety of Banti's disease. In these, as well as in the remaining two cases, he was able to demonstrate threads or strands of yellow hue, which he believed he was able to differentiate from tissue structures and recognize as streptothrix infection. Cultures which were made from one case were negative.

In 1915 Sprunt reported another case of splenic anæmia in a man with a history of lues and malaria. The spleen had been removed at operation. Similar pigmented patches were found among the enlarged trabeculæ, and microscopic deposits of iron and calcium were demonstrated similar to those in his previous case. Somewhat similar observations had been made in 1902 by Hektoen. He observed a process of degeneration in the elastic fibers, with subsequent incrustation with iron salts, in areas of subacute inflammation. These altered fibers were at times incorporated within giant cells. In one of the drawings of these deposits, he shows a structure very similar to the "streptothrix" described by Gibson.

Our attention was called to a similar finding in which, with the application of the simple stains alone, it appeared that we were dealing with a streptothrix or with the mycelial threads of the hyphomycetes.

The specimens were obtained from a man 46 years old, who for several years had suffered from diabetes. At autopsy, the case illustrated one of bronzed diabetes, in which the hæmato-

chromatosis had involved many organs. The most marked deposit of the rusty pigment was found in the spleen, mesenteric lymph nodes, liver, pancreas and heart. As the case will be more fully discussed in a study upon bronzed diabetes, I shall not go into the details of the history or the pathological findings, save those of the spleen and lymphatic glands.

The spleen was of normal size and its capsule was thin and somewhat wrinkled. The tissues were flabby and on section they appeared quite dark with occasional rusty areas. The Malpighian bodies were visible. The pulp substance was not easily broken, but there was no definite evidence of fibrosis. The rusty areas were few in number and consisted of small irregular patches. No direct association of these areas with vascular channels could be made out.

Calcareo-Ferruginous Deposits in Lymph Gland.

The mesenteric lymph nodes and particularly those about the head of the pancreas were a little enlarged, soft and tough. Each node was of a rusty brown color. The tissues about these lymph glands showed no evidence of pigmentation.

The lymph nodes on section showed a diffuse fibrosis throughout their structure and a peripheral thickening of the capsule. Unusually heavy trabeculæ entered the gland from the capsule inwards; thus the more marked fibrosis was in the periphery of the gland. The follicular arrangement of the node had been lost and the lymphocytic elements were scattered diffusely without arrangement between the trabeculæ and the reticulum. Where the fibrous tisue was laid down in heavier masses it had a very hyaline appearance and showed very few connective-tissue cells. Scattered throughout the gland structure was a heavy deposit of golden-brown pigment. This pigment was granular, varying from fine irregular dust-like particles to larger aggregated masses formed by the welding together of many small granules. The greater amount of the pigment lay free in the interstices of tissues, but some of it had been phagocyted by endothelial cells.

Aside from the remarkable deposit of granular brown pigment which was found to be iron-containing, there was also a unique appearance in the hyaline trabeculæ. In places a deposit of the iron-containing pigment was found within the clefts of this tissue. The deposits were molded into intricate forms identical in appearance with a coarse mycelium or the strands of a streptothrix. These structures showed beautiful transverse segments and not uncommonly club formation at the ends of the strands. In several places, however, one could still make out the individual granules entering into the formation of the more solid segmented strands. Branchings were frequently present, so that divisions, somewhat comparable to those of the penicillium, were found.

Although it appeared evident that all of these fungus-like structures had a common mode of origin, it was evident that some had undergone changes in their composition. Where these molded strands were in process of formation, their character was similar to that of the individual iron-containing granules which were diffusely scattered in the gland tissue. The Nishimura tests for iron were positive, both for the individual granules and also for the streptothrix-like structures. There was, however, some difference in the intensity of the reaction, in that the molded strands were of a lighter color, even blending into a greenish yellow. Furthermore, it was found that with the ordinary hæmatoxylin stain, irregular masses (by no means all) of the streptothrix-like strands gave a dark purple reaction, which shaded off into a lighter wine color. Some of the strands did not take the hæmatoxylin stain. Likewise, too, the application of aniline stains led to a partial coloration. The structures, however, did not stain by Gram's method. With silver nitrate a great number of these structures became black and were sharply outlined from the surrounding brown granules. When sulphuric acid was used, a few acicular crystals of calcium sulphate were formed. From the use of dilute mineral acids no gas bubbles were obtained. After the removal of the calcium and iron there remained a transparent hyaline matrix.

Besides these curious structures, there were other linear masses which could be distinguished from those above described. Whereas the former were found to occur in the interstices of the hyaline stroma, the latter had their origin within the more solid structures, at times in the vicinity of blood-vessels. In these there was a primary change of the tissue-matrix with a varying deposit of calcium salts. In these, fine elastic fibrils that coursed through the tissue stroma were demonstrated by Weigert's method, and evidences of varying degrees of degeneration with more diffuse staining of the fibers were obtained. They entered into the tangled structures in which calcium salts were readily demonstrable. In these calcified strands one could not see any pigment granules, and with ordinary or elastic-tissue stains one could not recognize any coloring suggesting an iron-content. Here again, however, the

Nishimura test showed the presence of a diffuse iron reaction, as if the iron salts had been diffusely absorbed in these areas of calcification.

Although it was noted that elastic fibrils in stages of degeneration entered into the bands of ferruginous calcification, these could not be demonstrated in all instances. At times the thickened trabeculæ of the lymph gland showed a homogeneous hyaline character which, with the elastic stains, gave a diffuse and relatively pale reaction. Frequently no true fibrils were present, but only a washed or blotchy elastin reaction was obtained. In these areas iron was commonly demonstrated and occasionally small granules of calcium salts.

Similar structures were observed in the spleen. These in part were aggregated in the trabeculæ about the blood-vessels and were like those described by Sprunt. Others, found in narrow spaces in the pulp substance, resembled more closely the segmented masses observed in the lymph glands and described by Gibson in one of his cases.

It is evident that in the above case we are dealing with two different kinds of calcium and iron deposits. On the one hand, we have a primary deposition of calcium in elastic fibers with a secondary absorption of iron. In these instances, the deposit of calcium is more extensive than that of iron, and many calcified strands can be found in which iron is not demonstrable. Wherever calcium impregnation of the elastic fibers is noted, a preceding process of degeneration can readily be made out.

The other deposit appears to have no relationship to a primary calcification of tissue structures. Here we are dealing with an ususual abundance of iron-containing pigment which lies in the tissue interstices and gradually becomes molded within the spaces. Wherever the neighboring masses incompletely fuse, evidence of apparent segmentation becomes prominent. Thus chains, like threads of large bacilli, are formed. In these structures, the appearance of calcium salts follows the fusion of the iron-containing granules. No calcium was demonstrable in the original granules and it was only seen in those masses which had fused into clear yellow threads.

The material we were dealing with had been fixed in formalin, and to it the criticisms of Hueck might apply. Hueck claimed that the presence of iron in areas of calcification or in bone, as was demonstrated by Gierke, was the result of an artefact; he claimed that either the fixative contained impurities of iron or that the solution of hæmoglobin in the fixative would tend to deposit its iron constituents in the calcified areas. However, under the conditions of the disease here studied (bronzed diabetes), in which enormous quantities of iron-containing pigment were diffusely deposited in the tissues, the opportunity for impregnation of the areas of calcification before death was constantly at hand. Moreover, the precipitation of iron-containing granules, which became closely massed and eventually formed aggregated cylinders, led to a foreign body mass in which the iron constituent was a prominent part. Under what conditions the calcium salts were attracted to these deposits is not clear, but it was evident that it was a late occurrence.

Our interest in this subject was further aroused by observing the simultaneous deposit of iron and calcium in the arteries. The calcified plaques of the aorta were examined in five cases with negative results. The peripheral scleroses with calcification (iliac, femoral, tibial, splenic) were also analyzed in 10 cases, and three of these were shown to have a deposit of iron within areas of calcification. These deposits are of interest in indicating that the iron had originated from the blood. Two of the specimens were obtained from elderly individuals (64 and 65 years) having senile gangrene of the foot, and one from a man aged 35 years having diabetic gangrene of the foot and leg.

Advanced processes of calcification, and areas where the degenerative process in the arterial wall acts as an irritant, not uncommonly show the development of a granulation tissue about their periphery. The capillary vascularity of these areas varies greatly, and where the stroma is loose small hæmorrhages are prone to occur. This we observed about the medial calcareous masses in each of the arteries obtained from the cases of senile gangrene. Not only did the border of the calcium deposit show the presence of granulation tissue, but an osteoid structure was also present at various points about the mass. Amidst the capillaries was a loose fibrous stroma in which more or less blood pigment was also demonstrated. In two cases the calcium deposits had, for the most part, involved the media, while lesser masses were found in the intima. In all three, calcified elastic bands were found in the zone between the intima and media, and others showing a similar degeneration were scattered between the muscle fibers of the media. An iron reaction was obtained in the calcareous deposits of the media as well as in the brittle elastic fibers associated with this degeneration. In the areas of advanced calcification the reaction was quite diffuse. The deposits of blood pigment and the neighboring elastic fibers also showed the presence of iron.

The third artery showed plaques of calcification in the thickened intima, while the original lumen was occupied by an organized thrombus. Vascular spaces were still present in the organized mass, while in the more solid areas of fibrous tissue deposits of blood pigment, representing the remains of the former blood clot, were readily recognized. Some of these pigment deposits were close to the calcareous masses. On application of the test for iron, not only was a positive reaction demonstrated in the deposits of blood pigment, but a diffuse reaction, more intense in the periphery, was also obtained in the calcareous plaques and in the calcified internal elastic lamina.

In these calcified structures the reaction showed that the iron was present diffusely and in granules. There was no evidence to indicate that the process of calcification had followed the deposition of blood pigment, or that the iron had been obtained from the tissues in which the calcium salts had been precipitated. Many calcified elastic fibers were seen in which iron could not be demonstrated. On the other hand, no iron-containing elastic elements were found in the absence of calcification.

In all of the cases here reported the deposit of iron occurred in calcareous masses under conditions in which there was a

local or systemic destruction of blood. In all instances the blood pigment (hæmosiderin) was deposited directly in the tissues, in which subsequently a mixture of iron and calcium salts was found. Similar observations on the impregnation with iron of tissues about old hæmorrhages have been made by S. Ehrlich and others. The presence of iron impregnation, through the agency of blood iron, in areas of previous calcification is in itself not unique. Whether, however, elastic fibers of arteries and organs may, in the absence of calcareous degeneration, absorb iron, as has been suggested by others, was not definitely determined in our material. It is, however, important that the development of pseudomycelial structures through the fusing of masses of blood pigment be recognized and distinguished from infecting micro-organisms. These fungus-like structures receive their calcium component late in their development, and many were found without this element.

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NOTES ON NEW BOOKS.

What to Eat and Why. By G. Carroll Smith, M. D., of Boston, Mass. Second edition. Thoroughly revised. Cloth, $2.50 net. (*Philadelphia and London: W. B. Saunders Company. 1915.*)

Dr. Smith says in the preface of his book: "If 'What to Eat and Why' simplifies dietetic therapy for the medical student and makes it chief among therapies for the busy practitioner, stimulating him to prescribe a dietetic therapy as readily as an electro-, hydro-, serum or drug therapy, the gap I have observed will be filled."

A thorough knowledge of disease and an intimate acquaintance with the physiological and pathological physiological action of foods in the body, both in the alimentary canal, as well as after absorption, are the requisites for any physician who wishes to practise dietetic therapy successfully. The mere prescription of "a dietetic therapy as *readily as* a drug therapy" will not further the idealistic aims of most physicians or accomplish the greatest amount of good.

In the book at present under consideration, so much has been left unsaid, that the subject becomes extremely simple. This extreme simplicity, however enticing it may be to those looking for practical information in this field, entails slipshod methods that will not be crowned with success. Careful diets, in which the caloric values of all the foods, as well as the proportion of the fats, proteins, carbohydrates and alcohol are painstakingly tabulated, are not furnished in as great a profusion as the modern treatment of obesity, diabetes, typhoid fever, etc., demands. Such qualitative diets as are given under nephritis, in which half of the articles of food mentioned are eggs, meat or fish, and yet the directions call for a limitation of protein intake, suggest that possibly all of the diet lists have not been thoroughly considered. The disturbance of function upon which the principles of dietetic therapy depend are taken up one by one and are fairly inadequately discussed. Very loose statements, as, for instance, that the tendency to gout, obesity, diabetes and arthritis, is increased by the excessive use of alcohol, coffee and tea, also by grief, financial loss, worry, or depressing weather; as well as others that are erroneous, for instance, that metabolism is diminished by the drinking of large quantities of water, are frequently found.

The contents, as well as the title of "What to Eat and Why," are designed to appeal to popular demands. The book will not fill the need of those desiring a well-balanced knowledge of either theoretical or practical dietetics. H. O. M.

Pathological Technique. By Frank Burr Mallory, A. M., M. D., and James Homer Wright, A. M., M. D., S. D. Sixth edition. Revised and enlarged. 536 pages. 174 illustrations. Price $3.00. (*Philadelphia: W. B. Saunders Company. 1915.*)

The invariable presence of this book on the shelves of laboratory workers in pathology and bacteriology attests its usefulness. By the selection of anatomical and bacteriological methods which it contains, the volume makes available the critical assistance of its experienced authors, and by a combination of lucid diction with intelligent typography it presents its information in the most accessible manner. In the past, the authors and publishers have been felicitated upon this book; a new measure of praise may be added in appreciation of the present edition.

The chapter on Bensley's methods for demonstrating mitochondria and cytoplasmic granules will be welcome to those who are interested in the newer studies of cellular states. The section on bacteriology and parasitology, with its additional paragraphs on blastomyces and streptothrix, brings this very satisfactory part of the book well up to the needs of the present lines of investigation.

Critical examination of the text reveals only a few incorrect statements and not many errors of omission. Among the former the line on page 66 may be mentioned for correction, where the words "pulmonary vein" are used instead of "pulmonary artery," in the description of the ductus Botalli. On page 137, the authors advise the use of "sterile defibrinated blood" for the preparation of blood agar. A simpler and more satisfactory method is the older one of Schotmüller—in which the blood is drawn into a 2 per cent solution of sodium citrate and thence poured into the agar-medium. The paragraphs on the Widal or "clump reaction" for the diagnosis of typhoid fever as set forth on pages 167-169 would be more adequate if they contained definite reference to the dilutions of serum to be used. The authors consider agglutination of organisms by a serum diluted 1 to 50 as a specific reaction. Many authorities, however, set 1 to 100 as the necessary titer of such a reaction. The section on the cultivation of typhoid bacilli from the feces (page 170) could be improved by a description of Russell's medium. The use of Russell's and Endo's media has given great satisfaction in this laboratory in the differentiation of intestinal organisms.

On page 476, the authors advise the use of the Noguchi butyric-acid reaction in testing spinal-fluid globulin. Most laboratories, in practice, employ either the Pandy or the ammonium sulphate test (the so-called Ross-Jones test) for this purpose. These tests are as satisfactory as the Noguchi reaction, and have no disadvantageous odor.

The last 69 pages of the book contain an assortment of paragraphs on methods for the examination of various materials—from the investigations to be made for animal parasites in the blood and feces to the technique of serological reactions. This compendium of what is known as clinical microscopy is under the caption "Histological Methods"—which is the title at the top of each page of this section. Few of the methods, however, are histological, and some of the descriptions are not sufficient to impart the whole method discussed. Among the latter may be mentioned those on

the Wassermann reaction and Lange's gold chloride test. The description of the Wassermann procedure, written by Drs. Hillman and Burgess, is admirably concise, but it is doubtful whether one without considerable experience could find these paragraphs of great value. Their presence in the book suggests the possibility of their being included in order to popularize the treatise, at a time when there is a general tendency to regard any practitioner as competent to conduct these intricate tests. The obvious dangers of false conclusions which may be drawn by men who have been emboldened by a too facile explanation to attempt the performance of these reactions urge that precautionary statements should be emphasized in these relatively brief outlines of the procedures. Serological methods, moreover, have no place on pages devoted to histological methods. Possibly it would be better if parts of this section were distributed in the general matter on parasitology, under appropriate headings, or separated in an appendix.

S. B-J.

A Treatise on the Principles and Practice of Medicine. By ARTHUR R. EDWARDS, A. M., M. D. Third edition. Thoroughly revised and rewritten. Cloth $6.00. (*Philadelphia and New York: Lea & Febiger, 1916.*)

In this third edition of his book the author has effected a reduction in the number of pages and incorporated the advances in clinical medicine since the last issue. The large space devoted to therapy reflects the trend of interest in this direction and also the author's personal views and experiences. This personal side of practice forms the principal excuse for the multiplication of text-books essentially alike.

T. R. B.

The Basis of Symptoms, the Principles of Clinical Pathology. By DR. RUDOLPH KREHL. Authorized translation from the seventh German edition, by A. F. BEIFELD, PH. B., M. D. Third American edition. Cloth $5.00. (*Philadelphia and London: J. B. Lippincott Company, 1916.*)

The reappearance of Krehl's invaluable "Pathologische Physiologie" in a new and enlarged translation of the seventh German edition is evidence of the well-merited approval it has won from the profession in America. The new title harks back to the first German edition and draws attention to the practical character of the work.

Dr. Hewlett, who was the first to translate this work into English, and who saw the second American edition through the press, writes a preface to the present volume.

The importance of physiological thinking and the recognition of disturbed function as the basis of symptomatology are hard to overemphasize; and American teachers and students are recognizing these facts more broadly each year.

Krehl's book is without a peer in this field; and this new edition in English brings it up to date and has incorporated in it much of the latest work of our own investigators.

The text is good and the literature well arranged in sections. Every thoughtful student and practitioner will wish to have it in his working library.

T. R. B.

Surgical Operations with Local Anesthesia. By ARTHUR E. HERTZLER, A. M., M. D., PH. D., F. A. C. S. Surgeon to the Halsted, Swedish and General hospitals, Kansas City, Mo. Second edition. 327 pages. 173 illustrations. Cloth $3.00. (*New York: Surgery Publishing Company.*)

The rapid sale of the first edition covering minor surgery, and the demand for a more complete work upon the subject, covering both major and minor surgical work, has induced Dr. Hertzler to present this second volume, which for completeness as to detail and for its low price places it, we believe, in a class by itself among the text-books upon this most interesting and growing subject.

Dr Hertzler's vast surgical experience and his work with local anesthesia constitute him an authority upon this subject; and the second edition of his book places within the hands of the doctor a manual which, for completeness and comprehensiveness, particularly recommends it.

The author seems to have overlooked no point of major or of minor importance. The large number of illustrations fully supplement the text; and both the general practitioner and the surgeon will appreciate this work as a reliable guide in their operations under local anesthesia.

A Text-Book of Pathology. By ALFRED STENGEL, M. D., Professor of Medicine, University of Pennsylvania; and HERBERT FOX, M. D., Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania. Sixth edition. Reset. 8°. Cloth $6.00; half morocco, $7.50. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

The fact that this book has gone through five editions is in itself a sufficient evidence of its value. The authors asd publishers furnish a product of over 1000 pages, conforming in every way to the usual profusely illustrated and well-indexed text-book of pathology, which at the end of a brief presentation of a topic leaves no doubt in the reader's mind, no room for argument, and no bibliography of the newer or conflicting views on the subject. This is a type of work which attempts to include every phase of the subject, and certainly a "short, readily comprehended, and even somewhat dogmatic, presentation of a subject" is most welcome to many. Such a presentation, however, to be of real value, can only be the product of those who are familiar with every phase of the subject in all of its details; unfortunately, pathology has outgrown the 'one-man' type of text.

M. C. W.

Short Talks with Young Mothers on the Management of Infants and Young Children. By CHARLES GILMORE KERLEY, M. D., Professor of Diseases of Children, New York Polyclinic Medical School and Hospital; Attending Physician to the New York Nursery and Child's Hospital, etc. Third edition. Revised and enlarged. Illustrated. $1.00. (*New York and London: G. P. Putman's Sons, 1915.*)

This is a very excellent little volume. It gives in a concise, clear and fairly complete form sound advice and directions to mothers and nurses as to the management of their infants and young children.

The discussion of the symptoms of disease are simple and clear. Suggestions for actual medical treatment, as is stated in the preface, are avoided, but the advice given is very practical and should help to fill a very definite want of the average mother or nurse.

"What Every Mother Should Know about Her Infants and Young Children," by the same author, published by Paul B. Hoeber, 67 E. 59th Street, New York, is an abstract of the above volume. Although far shorter than the original, it contains all the essential features of the former, and its very reasonable price (35 cents) should bring it into the hands of many who are unable to purchase the larger volume.

Either book should be a valuable addition to the armamentarium of the visiting nurse, dispensary doctor and social worker, in their efforts for the medical education of the masses.

H. W. W.

Differential Diagnosis, Volume II. Presented Through an Analysis of 317 Cases. By RICHARD C. CABOT, M. D. Cloth $5.50. (*Philadelphia: W. B. Saunders Company, 1915.*)

In this, the second volume of "Differential Diagnosis," Cabot follows the same plan as that used in the first volume, that is, he discusses in considerable detail various symptoms of importance through an analysis of cases presenting the symptom in question,

317 cases in all being analyzed in this volume. The major portion of the work is devoted to signs and symptoms referable to the abdominal cavity, and the organs contained therein—tumors, diarrhea, dyspepsia, hemetemesis, melena, and ascites being considered in this connection. In other chapters he studies by the same methods vertigo, glandular enlargement, swelling of the face, of the arms and legs, hemoptysis, fainting, hoarseness, pallor, delirium, palpitation, arrythmia, tremor, polyuria and frequent micturition. The cases are presented with the clearness for which the author is distinguished, and in a style which makes the reading of the book a real pleasure. As to its value as a method for teaching students there may be some doubt, but there is no question that it should prove of the greatest help to general practitioners, as well as to special workers in the various fields discussed, in refreshing their minds as to the multiplicity of causes of many of the common symptoms met with, and the importance of investigating every system in the body, however remote from the apparent source of the trouble, before a diagnosis is warranted.

T. R. B.

Diarrheal, Inflammatory, Obstructive, and Parasitic Diseases of the Gastro-Intestinal Tract. By SAMUEL G. GANT, M. D., LL. D. Cloth $6.00. (*Philadelphia: W. B. Saunders Company, 1915.*)

In this book of more than 600 pages Gant reviews the subject of the various conditions accompanied by diarrhea, including those associated with inflammatory or obstructive conditions in the gastro-intestinal tract. After touching upon the method of classification, which is very exhaustive, and calling attention to procedures of value in examination and diagnosis, he discusses the diarrheas met with in various organic diseases, in acute contagious diseases and in various metabolic diseases, the diarrheas in diseases not often encountered by us, such as sprue, hill diarrhea, typhus fever, and various other forms of the tropical or the subtropical types. A short chapter is devoted to the diarrheas due to faulty habits of life, and to the various forms due to disturbances in the secretions or in the innervation of the gastro-intestinal tract. Next he deals with diarrhea due to poisonings, paying especial attention, of course, to those due to decomposed foods. A number of short chapters then follow on the various forms of diarrhea met with in the various entero-colitides—tuberculous, luetic, amœbic, bacillary, gonorrheal, etc. The chapters on obstructive or surgical diarrheas and the post-operative diarrheas form a very interesting series, and these are followed by four chapters on the different procedures in the surgical treatment of the various forms of diarrhea—cœcostomy, appendicostomy, appendicocecostomy, colostomy, colectomy, etc. The book has many points of really great value to workers in this field, but is somewhat long and goes too much into detail to be of much value to the general practitioner except as a reference book.

T. R. B.

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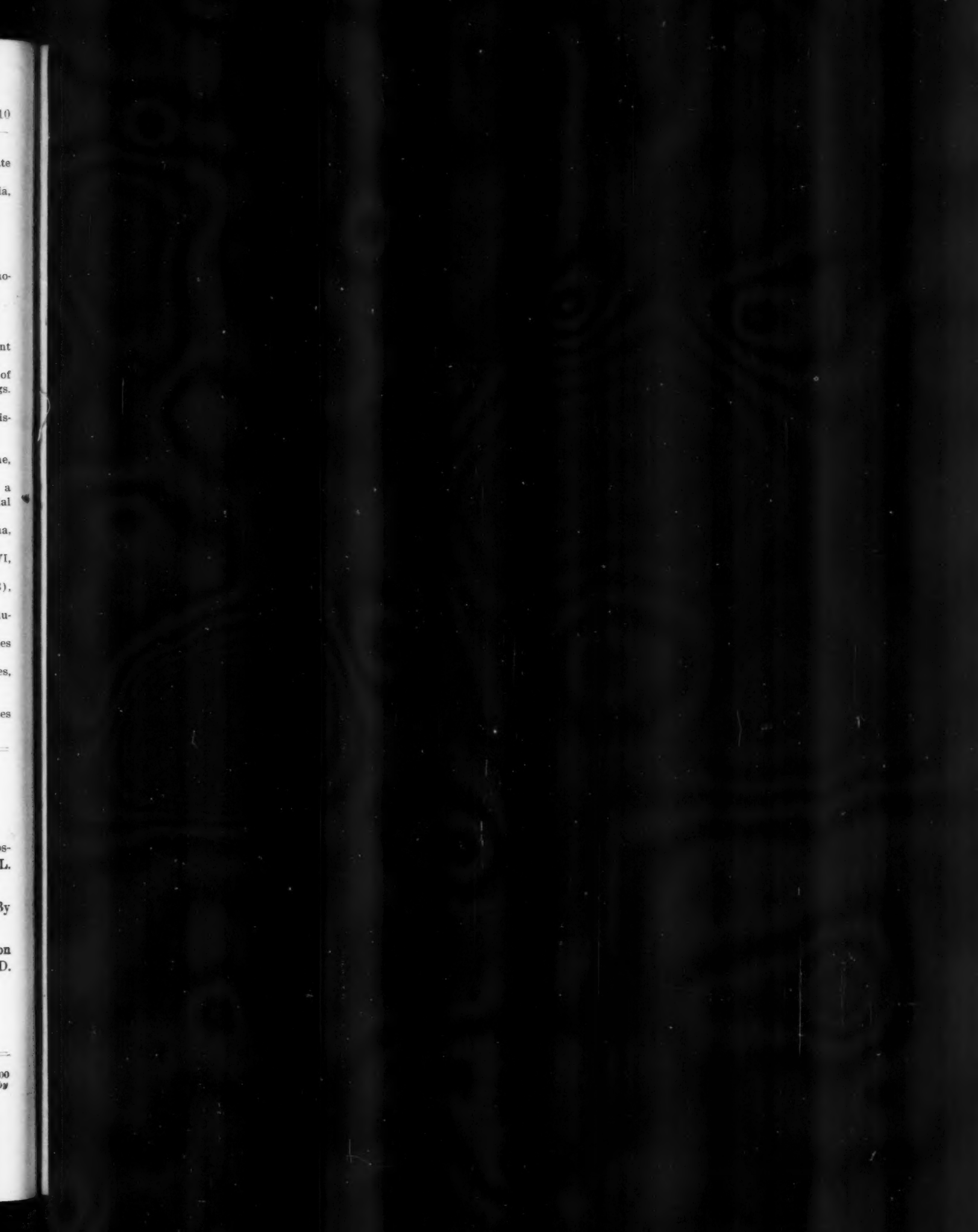
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